The role of long- and short-term typical dose, concurrent alcohol consumption and executive processes in ecstasy-related prospective memory deficits.

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A thesis submitted in partial fulfilment of the requirements of The University of Central Lancashire for the degree Doctor of Philosophy.

January 2014

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School Psychology

Acknowledgements

I would like to thank The School of Psychology at The University of Central Lancashire for their support and funding over the last three years. I would also like to thank Dr. Jeannie Judge, Dr. Sarita Robinson and Prof. John Fisk for their guidance, support and advice throughout the project. They have provided feedback on the drafts of several papers and chapters throughout my programme of study and I am entirely grateful for this. Prof. Fisk's mentorship over the last three years has been invaluable and he has always been on hand to point me in the right direction. I owe a lot to Dr. Cathy Montgomery for her help with the recruitment of participants and for allowing me to use the laboratories at Liverpool John Moores University. Finally, I would like to thank my parents for their emotional and financial support during this period.

Abstract

Building on previous research demonstrating prospective memory (PM) deficits in ecstasy users the purpose of this thesis was to explore the specific nature of these deficits focussing on establishing dose related effects and exploring possible mediators. Using laboratory-based measures of PM and a detailed background drug use questionnaire, the extent to which the typical dose of ecstasy per session can predict PM performance was examined. In Chapter 7, increased dose of ecstasy per session (typical dose of ecstasy per session in the 12 months prior to the test-session) was associated with poor short-term time-based PM performance. Chapter 8 examined the effects of concurrent alcohol and ecstasy use on PM performance. The use of alcohol and ecstasy together was not associated with additional PM performance deficits. Chapter 10 investigated the role of executive functioning processes in accounting PM deficits in ecstasy users. Verbal word fluency, updating, shifting and inhibition executive functions did not predict PM performance in ecstasy users. Chapter 11 used correlational analyses to investigate the effects of long- and short-term indicators of ecstasy, cannabis and cocaine use on PM performance. Clear relationships were established between long-term indicators of ecstasy and cocaine use and PM performance. Total lifetime ecstasy and cocaine consumption and the long-term average dose of ecstasy and cocaine per session were related to PM performance. For both drugs, increased lifetime consumption and larger doses consumed in a typical session were associated with adverse outcomes on PM tasks.

PM impairments in ecstasy users were found in all studies in this thesis. These findings have important implications for those individuals who use ecstasy. Firstly, the use of ecstasy is detrimental to PM performance and therefore can potentially be debilitating to normal everyday functioning. More specifically, those individuals who consume higher doses of ecstasy per session may be more likely to display PM impairments compared to those individuals who consume lower doses. This information should be used to educate ecstasy users as to the possible consequences of its use. Future research should further explore the importance of typical dose of ecstasy per session in relation to cognitive performance in general. In addition to the administration of laboratory-based measures of PM, the use of neuroimaging techniques could be employed. This would allow researchers to potentially identify specific brain regions that may be implicated in PM deficits in those ecstasy users who consume large doses of ecstasy in a representative session.

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Chapter 1: Overview of thesis

Chapter one provides a brief overview of the thesis. Chapters 2, 3, 4, 5 and 6 are all literature review chapters. Chapter 2 provides an introduction and a general background to prospective memory (PM) and the realisation of delayed intentions. Chapter 3 identifies the different brain regions that are implicated in event-and time-based PM tasks and investigates the extent to which these areas are affected by the use of licit and illicit drugs. Chapter 4 discusses the neurotoxic potential of licit and illicit drugs. Particular attention is given to the effects of cannabis, ecstasy and cocaine on the neural system. Chapter 5 describes a range of self-report and laboratory-based objective measures of PM that are commonly used in the literature. Issues of reliability and validity are also discussed. Chapter 6 provides a detailed overview of the effects of licit and illicit drugs on PM. Chapters 7 and 8 detail the first empirical chapters of this thesis. Chapter 7 investigates the effect of the typical dose of ecstasy consumed in representative session on PM performance. Chapter 8 explores the extent to which concurrent alcohol and ecstasy consumption can impair PM performance. Chapter 9 contains a further literature review that provides a detailed overview of executive functioning (EF) and its relationship with PM. Chapter 10 is the third empirical chapter and investigates the extent to which underlying impairments in EF processes (verbal word fluency, updating, shifting and inhibition) can explain PM deficits in ecstasy users. The Chapter also seeks to evaluate whether the effects of ecstasy on PM were independent of any effects associated with verbal word fluency, updating, shifting and inhibition. Chapter 11 is the final empirical chapter where correlational analyses are used to explore the relationships between long- and short-term indicators of ecstasy, cannabis and cocaine use and PM performance outcomes. Chapter 12 is a general discussion of the results and evaluates the findings in terms of the implications for ecstasy users and the implications for the future study of PM and other cognitive processes.

Chapter 2: Defining prospective memory: The realisation of delayed intentions

Chapter Outline

The present chapter outlines a distinct cognitive ability that is commonly known as prospective memory. The construct of intentions is introduced with the aim of providing an explicit definition of delayed intentions. Different approaches to and models of prospective memory are discussed together with the potential role of retrospective memory in everyday prospective remembering. Different classifications and frameworks of prospective memory (PM) are outlined in order to provide a thorough insight into the subject. Particular attention is given to the retrieval phase and in particular to the underlying differences between event- and time-based PM.

2.1 Intentions

When people complain of having problems with their memory, they do not often refer to difficulties they have in remembering things that they did the previous day or remembering stories that they had heard on the news. Rather, they commonly refer to forgetting to carry out everyday tasks such as remembering to take medication or remembering to attend appointments (see Kliegel, Jäger & Phillips, 2008). These types of real-world memory lapses whereby one forgets to carry out previously formed *intentions* in the future are known as prospective memory (PM) failures (Meacham & Singer, 1977). Since PM primarily concerns the forgetting of *intentions*, it is important to briefly consider the nature of intentions. For example, what are intentions and how do they relate to human behaviour? (Kvavilashvili & Ellis, 1996). The answers to these questions will potentially improve our understanding of the underlying processes involved in PM tasks.

Intentions are a key feature of the activities and tasks performed in our everyday lives. However, providing a single definition of an intention is difficult given the wide variety of intentions we carry out on an everyday basis (Gauld & Shotter, 1977). Kvavilashvili and Ellis (1996) describe intentions as a person's *readiness to act* at some point in the future. It is this *readiness to act* that governs the decision *that* is made to carry out an intention (Ellis, 1996). Aside from this, several other aspects of intentions should be also be acknowledged including *what* (i.e., the retention of an action), *where* (i.e., location or place associated with an action), *when* (i.e., when the memory for an action should be retrieved), *who* (i.e., with, to or from

whom) and *how* an intention might be retrieved (actions associated with satisfying an intention).

There are two main types of intentions; *prior intentions* where an intention is formed before an action and *intentions in action* where an intention is formed spontaneously with little time to plan for an action. A definitive feature of a prior intention is that they occur following a conscious decision to carry out behaviour (Brand, 1984; Heckhausen & Kuhl, 1985). It is not possible for a prior intention to be formed unless a person has made a conscious decision to act. There are two further subcomponents of prior intentions – *Immediate actions* refer to intentions that can be carried out shortly after the conscious decision has been made to act. In contrast, *delayed intentions* involve a delay between the decision to act and any actions directed towards the fulfilment of an intention (Gauld & Shotter, 1996). The term PM can also be used to describe the underlying processes and mechanisms involved in the retrieval and subsequent fulfilment of a delayed intention (Kvavilashvili & Ellis, 1996).

2.2 The realisation of delayed intentions

The ability to form, retain, recall and realise intentions is fundamental to everyday functioning (Baddeley & Wilkins, 1984; Ellis, 1996; Ellis, Kvavilashvili & Milne, 1999 Harris, 1984). Thus, it is interesting to note that up to 70% of everyday memory failures are concerned with the forgetting of an intention (Terry, 1988). In many cases, intentions can be performed immediately after they are formed. However, there are times when intentions must be postponed and carried out at some point in the future. For example, if we are asked to pass on a message to a friend when we see them, we may not be able to pass on the message until we next meet that person. PM (Meacham & Leiman, 1982) or the realisation of delayed intentions (Ellis, 1996; Ellis & Kvavilashvili, 2000) refers to the process whereby intentions are formed and carried out at some point in the future. As a result, successful prospective remembering is dependent on the recall of content and its retrieval at an appropriate time for action (Ellis & Kvavilashvili, 2000).

According to Ellis and Kvavilashvili (2000), PM tasks can be identified by the following three characteristics. First, PM tasks involve a delay between the formation of an intention and its fulfilment. For example, an appointment with a doctor may have to be arranged several days in advance. Second, PM tasks do not involve an explicit reminder to

perform the intention. Using the same example, the doctor surgery will not often remind people that they have an appointment. Finally, a person may need to interrupt ongoing everyday activities and tasks in order to successfully perform an intended action (Ellis & Kvavilashvili, 2000). In this case, there may be a need to interrupt an ongoing job-related task (e.g., attending to work emails or filing) prior to attending the appointment with the doctor. In order to fulfil this intention, one's attention must switch from the ongoing task to thinking about the intended action and then fulfilling it (McDaniel & Einstein, 2000).

Despite being a distinct aspect of human cognition, PM is not entirely independent of other memory processes. Retrospective memory (RM) refers to processes associated with the recall of information and primarily concerns information related to *what* it is that has to be done (Cockburn, 1995; Einstein & McDaniel, 1996). Although the realisation of delayed intentions involves components of both RM and PM in that they both require the memory for content, they are separable with PM being reliant upon a self-initiated cue for retrieval. For example, a common feature of a laboratory-based RM task is the formation and encoding of an intention and action (Ellis, 1996). Einstein and McDaniel (1990) suggest that in an RM task an experimenter directs a participant's attention towards the retrieval of a previously experienced episode (Tulving, 1983). By contrast, PM tasks require people to remember to carry out an intention after a target event has occurred or after a period of time has elapsed. Thus in PM tasks, there is no specific request for a search of memory (i.e., from an experimenter) and rather, memory retrieval is entirely dependent on a person's ability to interrupt ongoing activities and perform an intended action (Einstein et al., 2005).

Ellis' (1996) conceptual framework is useful for explaining the different retrospective and prospective processes involved in the realisation of delayed intentions. The first stage of this five component model is focused on RM and relates to the processes associated with the retention of an action (i.e., *what* the intent is including well-learned or novel tasks), the intent itself (i.e., *that* conscious decision to carry out an action or the readiness to act), and the retrieval context (i.e., *when* the memory for an intention should be retrieved). The retrieval context identifies cues and characteristics that should prompt the initiation of an action at some point in the future).

The remaining four stages of Ellis' (1996) framework refer to various PM processes involved in the realisation of delayed intentions. The *retention interval* describes the delay between the formation of an intention and the initiation of an action. The delay period can

typically vary from several seconds to a number of minutes or hours and this has led to the classification of short- and long-term delayed intentions (Baddeley & Wilkins, 1984). *Retrieval* in a *performance interval* is a distinct stage, which is based on the realisation that a particular situation presents a retrieval context where an intention should be retrieved and performed. However, successful realisation can only occur if the perceived situation corresponds to the encoded retrieval context. A further stage examines how the *initiation and execution of an intended action* can influence its realisation. This is a complex stage that includes events that could potentially affect the outcome of a delayed intention such as distractions during the execution of an action or interference from unexpected extraneous circumstances. For example, an intention to return a book to the library might be interrupted after meeting a friend on the way or fail because the library is closed. In both situations, the intention has not been satisfied and thus, there is a requirement for the re-planning of an intention and the associated encoding of a revised retrieval context (Ellis, 1996). Stage five refers to the *evaluation of an action* and involves a comparative process between a goal state (information relating to *that, what, where, who* and *how* an intention is realised) and current state (i.e., the outcome of an executed or unexecuted intention; see Ellis, 1996; Newell & Simon, 1972). Evaluative processes maintain efficiency by ensuring that executed actions, which have satisfied a delayed intention, are not repeated. Further, they ensure that future actions are directed towards the recovery of earlier actions that have failed to satisfy a delayed intention (Ellis, 1996).

Another theory put forward by Shapiro and Krishnan (1999) further highlights the involvement of RM in the realisation of delayed intentions. Shapiro and Krishnan (1999) suggest that the memory for content of an intended action is retrospective whereas, actually remembering to carry out an intended action is prospective. The authors examined both components (retrospective and prospective) in situations where several intentions were present and investigated the extent to which important intentions affected RM and PM for less important intentions. Findings indicated that both retrospective and prospective remembering were better for more important intentions relative to less important intentions. However, influence of an important intention on memory for a less important intention was mediated by order of intention and type of memory component. PM was better for unimportant intentions that were completed before important intentions whereas RM was unaffected by order of intention. Aside from highlighting retrospective and prospective components of PM tasks, further findings from Krishnan and Shapiro's (1999) study suggest

that the retrospective and prospective components of memory are theoretically and empirically separable and may be mediated by different underlying processes.

Even so, if a person is impaired on RM tasks, some level of impairment may also be expected in PM. This assertion is supported by recent research that has identified an association between better RM and increased performance on PM measures (Hadjiefthyvoulou, Fisk, Montgomery & Bridges, 2011a). Furthermore, PM tasks with a high RM load have been shown to increase PM response times (Wang, Kliegel, Liu & Yang, 2008). Clearly, RM is an important aspect of prospective remembering, however, the remainder of this Chapter and indeed the later empirical work focuses solely on the prospective component of PM tasks.

2.3 Classes of prospective memory

Due to the complex nature of prospective remembering, a unified theoretical framework has not been established (Marsh & Hicks, 1998). However, in recent years, research has been directed towards the study of PM and different theoretical constructs have begun to emerge. An important question in the research surrounding PM is why people perform well in some situations but then fail to realise delayed intentions in other contexts. Possible reasons for performance differences can be drawn from the different classifications of PM that have been proposed in the literature (Kliegel, Martin, McDaniel & Einstein, 2004).

Kvavilashvili and Ellis (1996) suggest that PM can be distinguished according to four main phases of information processing including (a) the encoding phase (b) the retention phase (c) the retrieval phase and (d) the performance phase. Further distinctions of PM include PM proper and vigilance/monitoring (Uttl, 2008). PM proper involves bringing back to awareness previously formed intentions in the right context (*when* and *where* an intention should be retrieved). An example of PM proper is a person passing a message on to a friend when they next see them. If there is a long delay period between the formation of the original intention and when the person next sees their friend, it is likely that the intention will be temporarily suppressed. Thus, this PM task requires a person to bring the intention (i.e., passing on a message) back into conscious thought upon the presentation of the PM cue (i.e., seeing the friend). Vigilance/monitoring differs from PM proper in that the plan to execute a specific action remains in consciousness until the intention is fulfilled. For example, a train conductor maintains a plan to issue a set of instructions to train drivers and other train personnel. This plan is maintained in consciousness as the train conductor monitors for

specific PM cues (i.e., trains arriving and leaving the station, the platform being clear of people). When PM cues are recognised, the train conductor should deliver a set of instructions to drivers and other personnel (see Uttl, 2008).

Even though there is a clear difference between PM proper and vigilance/monitoring, PM studies rarely distinguish between the two. Nonetheless, a basic understanding of the fundamental differences between the two might be useful to identify the specific PM task (PM proper or vigilance/monitoring) used in particular studies. Despite this, more explicit distinctions are commonly made in regard to the retrieval phase and the difference between event- and time-based PM tasks. This Chapter discusses the theory behind event- and time-based PM tasks and provides a detailed account of the different strategies that people may use for accurate PM retrieval. The empirical work in this thesis will use a number of laboratory-based event- and time-based PM tasks to explore PM deficits in ecstasy users.

2.3.1 Encoding

PM tasks can be identified according to the planning processes implicated during the initial coding of an intention. For instance, whether an intention is perceived to be important or unimportant, based on simple or difficult decisions, or generated by one or others can all affect PM performance.

Important and unimportant intentions

Task context and in particular, the perceived importance of a delayed intention is an important factor which can be used to explain performance differences across PM tasks. This proposal is based on the assumption that when forming an intention, a person will often make a subjective judgement based on the intention's importance. This assessment is dependent on several factors including the benefits or consequences of success and failure, respectively (Kvavilashvili & Ellis, 1996). In relation to this, it is plausible to suggest that people will perform better on PM tasks which are perceived to be important relative to those that are perceived to be unimportant (Kliegel et al., 2004). Consistent with this proposal, research has shown that perceived task importance has beneficial effects on PM performance (Kvavilashvili, 1987; Kliegel, Martin, McDaniel & Einstein, 2001; Kliegel et al., 2004; Meacham & Singer, 1977; Somerville, Wellman & Cultice, 1983).

Studies have shown that prospective remembering is highest for important appointments (Andrzejewski, Moore, Corvette, Herrmann, 1991) and highly interesting activities (Somerville et al., 1983). Similarly, Ellis (1988) found a positive relationship between the recollection of an intention and its perceived importance .One possible reason for this is that the encoding of a seemingly important intention produces a series of integrative and organisational processes which in turn provide several cues for the retrieval of a delayed intention (Kvavilashvili & Ellis, 1996). In adding further understanding to the role of task importance in prospective remembering, Meacham and Singer (1977) found that delayed intentions are more likely to be realised if they are associated with a high incentive. While there appears to be substantial support for the role of task importance on PM, some results suggest that the subjective importance of a delayed intention has no effect on its realisation (Goschke & Kuhl, 1993). Further, the early literature has failed to identify specific task conditions that might accentuate or attenuate the effect of task importance on PM performance. Later research, however, has indicated that task importance has a positive effect on time-based but not on event-based PM tasks (Kliegel et al., 2001). The authors propose that the increased attentional resources demanded by time-based PM tasks actually aid prospective remembering. The same effect may not have been found for event-based PM since there is an explicit cue for retrieval and thus, the same level of monitoring required in time-based tasks is not necessary. To test this proposal, the same authors (Kliegel et al., 2004) conducted another study whereby the attentional demands of event-based tasks were manipulated. Crucially, an importance effect was only found for event-based tasks that relied on demanding monitoring processes. Overall, the literature indicates that higher subjective task importance has a positive effect on prospective remembering especially on PM tasks, which demand increased levels of monitoring and attentional resources.

Intentions based on simple or difficult decisions

The decisions that operate prior to the formation of an intention can influence later realisation. For example, intentions can be formed following a simple or more difficult decision and as such, the planning processes associated with each can be different. Specifically, it is thought that simple decisions are likely to be followed by less complicated planning processes than those evoked by more difficult decisions (Kvavilashvili & Ellis, 1996). Similarly, intentions that involve the reorganisation of a previously planned activity or

the prioritisation of activities are likely require intricate attentional resources which then lead to the detailed processing of that intention.

Self- or other- generated intentions

During initial encoding, a delayed intention is either formed following a personal need to do something or after a specific request from another person. These are referred to as self-generated and other-generated intentions, respectively (Cohen & Conway, 2007; Ellis & Nimmo-Smith, 1993). The primary difference between the two is derived from the *origin* of the intention. For example, self-generated intentions follow an intrinsic need to do something. By contrast, other-generated intentions are based on extrinsic needs or instructions from others (see Kvavilashvili & Ellis, 1996). In this way, it is much easier for other-generated intentions to be tested within the laboratory since experimental tasks often require explicit instruction from an experimenter. Nonetheless, questionnaire studies have been used to test the effects of the origin of an intention on prospective remembering (Kvavilashvili & Ellis, 1996).

2.3.2 The retention phase

The length of the interval between the formation of an intention and the time when an intention should be retrieved from memory can further distinguish prospective remembering (Baddeley & Wilkins, 1984; Dobbs & Reeves, 1996). Two types of PM task have been identified alongside this proposal; short-term PM tasks, and long-term PM tasks. By way of illustration, the event or time which governs when an intention should be carried out might occur a short-time (e.g., several seconds or a number of minutes) after the intention was defined (short-term PM tasks), or several days, weeks, or months later (long-term PM tasks; Dobbs & Reeves, 1996**).** Evidence within the literature suggests that PM performance declines for PM tasks with longer delay periods (Brandimonte & Passolunghi, 1994; Meier et al., 2006).

Brandimonte and Passolunghi (1994) found significant declines in PM performance with increased delay periods between PM instruction and the presentation of a PM cue. Importantly, PM declines were found for delay periods as short as three-minutes suggesting that PM forgetting occurs in a relatively short time frame. One interpretation of these findings is that the memory processes associated with short- and long- delay intervals might be very

different (Dobbs & Reeves, 1996; McBride, Beckner & Abney, 2011). For example, the planning processes and monitoring strategies involved in meeting a friend in 2-minutes (short-term) might be qualitatively different from those required to realise an intention of meeting a friend in five days (long-term). In line with this proposal, Meacham & Leiman (1976, p.328) suggest that short-term PM tasks may be no different to "maintaining one's vigilance or attention". Kvavilashvili and Fisher (2007) propose that a person is likely to keep short-term intentions in their mind for short delay periods. For example, a person might maintain a short-term intention in memory by consciously thinking about the intention throughout delay period. By way of contrast, Einstein and McDaniel (1990) argue that long-term delayed intentions require extended periods of conscious awareness. This is because there is additional opportunity for the memory for an intention to dissipate over longer delay periods. For example, distractions in the environment or the completion of other tasks may detract attention from long-term intentions. Furthermore, since PM performance is dependent on the use of monitoring processes for accurate PM retrieval (Einstein & McDaniel, 2010), people may have difficulty in maintaining monitoring processes for longer delay periods.

Research indicates that declines in monitoring occur in the first few minutes after a PM intention has been formed (Brandimonte & Passolunghi, 1994; Einstein et al., 2005). Other studies suggest that monitoring processes decline over extended periods of up to 20-minutes (Loft, Kearney & Remington, 2008) and PM performance becomes worse as the retention interval is increased (Martin, Brown & Hicks, 2011). Nonetheless, the extent to which people use monitoring process to aid prospective remembering is highly dependent on PM task type. For example, focal PM tasks (see Chapter 2, Section 2.3.3.1) are suggested to require significantly less monitoring processes compared to non-focal PM tasks. This is because in focal PM tasks, the PM task is crucial to the stimuli which are processed in the ongoing task. For example, if the PM cue is a specific word, then the use of a lexical decision task or a category identification ongoing task would encourage focal processing of the PM cue. This is because the PM cue is directly processed as part of the stimuli encoded in the ongoing task. On the other hand, non-focal processing of a PM cue occurs when the PM cue is not directly processed in the ongoing task. For example, if a PM cue is a specific feature of a word (i.e., a syllable, the starting letter), then the use of a lexical decision task or a category identification ongoing task would encourage non-focal processing of the PM cue. In order to process the PM cue, a person is required to process additional information that is not required to complete the ongoing task (i.e., syllables and starting letters of each word). Thus,

compared to focal PM tasks, non-focal PM tasks are suggested to depend more on monitoring processes for retrieval (Einstein & McDaniel, 2005). Despite this, in Loft et al's (2008) study which used a focal PM task, monitoring process were still evident for time periods of up to 20-minutes. In summary, focal and non-focal PM tasks involve the use of monitoring processes for retrieval. Nonetheless, the extent to which monitoring processes are used in each task may be very different. For example, non-focal PM tasks rely more on a directed search for retrieval and thus depend more on monitoring processes compared to focal PM tasks (Einstein & McDaniel, 1996)

More recent research (McBride et al., 2011) has attempted to explore the nature of PM forgetting in the context of the retention phase. By manipulating the delay period between PM instructions and PM target presentations, McBride et al. (2011) were able to investigate the extent to which longer delay periods increase PM forgetting. PM performance was measured for delays of 2–20 minutes in Experiment 1 and for delays of 1–10 minutes in Experiment 2. Further manipulations included PM task type such that some PM responses were governed by focal PM cues and others by non-focal PM cues (see Chapter 2, Section 2.3.3.1). The results suggest that there was a rapid decline in non-focal PM performance for shorter delay intervals and a slower decline in non-focal PM performance for longer delay intervals (Experiment 1). No effect of delay period was found for the focal PM condition in Experiment 1 or Experiment 2. These findings suggest that in non-focal PM tasks, PM declines in a non-linear fashion such that there is a rapid deterioration in the initial stages of the delay period followed by a slower decline towards the end of the delay period. Given that PM retrieval in non-focal PM tasks is suggested to require attention demanding processes, it is possible that participants were engaging in high levels of monitoring at the beginning of the ongoing task but had difficulty in maintaining the same level of monitoring for more than a couple of minutes. Following an initial sharp decline in monitoring levels, monitoring levels become sustainable with much slower declines towards the end of the delay period. This interpretation of the findings is consistent with research which has found significant deterioration of monitoring levels within three-minutes of when an intention was first formed (Brandimonte & Passolunghi, 1994). Overall, there is conclusive evidence which indicates that PM performance declines in a non-linear fashion when the delay between PM instruction and PM cue presentation is increased (Brandimonte & Passolunghi, 1994; Loft et al., 2008; McBride et al., 2011). This is especially true for non-focal PM tasks that require self-initiated monitoring processes for retrieval (McBride et al., 2011).

2.3.3 The retrieval phase

The retrieval phase is a period during PM tasks where the opportunity for an appropriate response occurs. Kvavilashvili (1990) identified three main types of retrieval occasion; *event-based* (a delayed intention which is externally cued by the environment), *activity-based* (a delayed intention which is governed by an activity in which a person engages), and *time-based* (delayed intentions which are cued by the monitoring of time). Other researchers have argued that event- and activity-based intentions are very similar and as a result, there is no need to distinguish between the two (Einstein & McDaniel, 1990; also see Kvavilashvili & Ellis, 1996). Outlined below are the different frameworks and concepts surrounding event- and time-based delayed intentions.

2.3.3.1 Event-based prospective memory

Event-based PM tasks involve remembering to perform a specific action after an external event has occurred (Einstein & McDaniel, 1990). In terms of PM, an event is an episode which occurs as a result of a person, object or location (Kvavilashvili & Ellis, 1996). For example, if a person has to pass on a message to a friend, actually seeing that person (i.e., the event) may act as a cue for retrieval. Typical laboratory tasks which aim to investigate event-based PM involve an ongoing task such as judging whether two abstract patterns are the same (Fisk & Warr, 1996). Then, for a PM element, participants are typically asked to make a predetermined response (i.e., pressing a key) following the presentation of a target event during the ongoing task.

However, laboratory-based paradigms fail to capture the processes involved in complex PM situations. Ellis (1996) proposes that laboratory-based PM tasks do not account for the planning processes involved in real-life event-cued PM. For example, in real-life event-based prospective remembering, there is often a requirement to organise and plan several activities according to their subjective importance. Thus, some laboratory tasks make it difficult to investigate the full range of processes involved the planning and execution of event-based intentions. Despite this, other PM studies have used alternative PM tasks which aim to directly discriminate between the planning and execution stages of prospective remembering.

As discussed previously, Kliegel et al., (2000) used a complex six element task (see Shallice & Burgess, 1991) where participants were required to self-initiate six different subtasks

during a limited time period. Each subtask had to be scheduled and prioritised in such a way that would allow for the completion of as many subtasks within the time period. In an attempt to capture the planning processes associated with complex PM situations, participants were also asked to generate a plan for the execution of the six element task. This method is considered to closely reflect the active planning processes associated with real-life PM tasks. Moreover, this method allows for authors to separate the planning stage from the execution stage of PM tasks. Studies which have used this six element task have been able to clearly distinguish between the planning, initiation and execution stages of event-based PM tasks (Kliegel et al., 2000). A whole host of other laboratory based tasks have been developed to investigate event-based PM performance and these are discussed in detail in Chapter 6.

Theoretical models of event-based PM

Theoretical models of event-based PM aim to identify the underlying processes and mechanisms which allow people to successfully perform event-based PM tasks. Monitoring theories of event-based PM (Einstein et al., 2005; Guynn, 2003) suggest that after the formation of an intention, an executive attentional system such as the *Supervisory Attentional System* (SAS; Shallice & Burgess, 1991) monitors the environment in an attempt to identify a target event. If a target event is present, the SAS interrupts any ongoing tasks and initiates a series of processes associated with the retrieval of an intention. In relation to this, Guynn (2003) argues that laboratory tasks of event-based PM require a series of recognition checks to test whether a particular cue represents a target event or not. Once again, if a recognition check signals that a target event is present, the SAS triggers the retrieval of an intention. Monitoring theories (Einstein et al., 2005; Guynn, 2003) of event-based PM assume that the retrieval of an intention is a controlled process which places significant demand on preparatory processes during the performance interval (i.e., the period of time between the formation of an intention and the occurrence of a target event) (Smith, 2003). Findings which are consistent with this perspective have shown that dividing attention during retrieval has a negative effect on event-based PM performance (Einstein et al., 1997; Marsh & Hicks, 1998, Park, Hertzog, Kidder, Morrel & Mayhorn, 1997).

Additional findings which support monitoring theories of event-based PM show that task processing is slowed during ongoing tasks when people are required to concurrently search the environment for target events (i.e., a PM task; Smith, 2003). In an ongoing task,

Smith (2003) asked participants to make lexical decisions as quickly as possible. Then, to provide a PM element to the study, participants were asked to “press a key” when any one of six target events occurred. There were two experimental conditions; in condition one, participants performed only the on going task whereas in condition two participants performed the ongoing task and the PM task together. For people who performed the ongoing task and the PM task, task processing was slowed on non-PM target trials. Thus, even if a target event is not present, the recognition check/monitoring slows processing on the ongoing task. This is because significant resources are expended whilst people search the environment for a target event.

Although some PM tasks require effortful monitoring of stimuli for a target event, relatively little is understood about the specific monitoring patterns which are used by people to aid prospective remembering. For example, it is possible that there are individual differences in monitoring patterns used by different people. A recent study by Savine, McDaniel, Shelton and Scullin (2012) has identified three candidate models which characterise the range of monitoring processes used by different people; attentional focus, secondary memory retrieval and information thresholding. Each of the three models are largely based on theories of working memory and concern the active maintenance or manipulation of information in the focus of attention. Savine and colleagues (2012) conceptualisation of the monitoring processes involved in prospective remembering are in concert with the proposal that there is a significant link between working memory and PM (Brewer, Knight, Marsh & Unsworth, 2012; Rendell, McDaniel, Aberle & Kliegel, 2010)

The attentional focus model comes from one of the two working memory components put forward by William James (1980) and Unsworth and Engle (2006; 2007). The attentional focus model proposes that details of PM targets, requisite actions and other ongoing task demands are maintained in the focus of attention. Maintaining the PM intention in the focus of attention allows for the representation of the PM target to be compared to each individual stimulus within the environment. A one-to-one comparison between the current stimulus and each PM target is made until the PM intention has been carried out or until it is recognised that a PM response is not appropriate.

The Secondary Memory retrieval model is based on the second component of working memory (James, 1890; Unsworth & Engle, 2006) and, in contrast to the attentional focus model, the specific PM intention is not loaded into the focus of attention. Rather, a

more general memory trace is formulated which simply reminds a person that they need to do something at a specific point in the future. This allows people to proactively shift attention from the ongoing task to active attempts of retrieval of the specific details of the PM intention from secondary memory. If the initial attempt of PM retrieval is unsuccessful (i.e., as a consequence of complex environmental demands or PM stimuli) then further retrieval attempts may be necessary.

The information thresholding model is based on Cowan's (1995; 2005) embedded-process model of working memory which concerns the focus of attention and an activated portion of secondary memory. The information thresholding model suggests that ongoing task performance is maintained in the focus of attention while a PM intention is maintained in an activated portion of secondary memory which can be easily accessed without loading on attention demanding resources. As a result, no performance cost to ongoing task performance should be observed.

Savine et al. (2012) developed two experiments which attempted to demonstrate a) which of the three monitoring patterns are typically used by people to detect PM targets, b) which monitoring pattern leads to the greatest performance cost to an ongoing task, c) which of the three monitoring patterns produces the best PM performance, d) whether people consistently use the same monitoring patterns for PM tasks, and e) how task, personality and cognitive factors influences the use of different monitoring patterns. The Complex Ongoing Serial Task (COST; Savine et al., 2012) was used to categorise participants according to the monitoring strategies that they each used for retrieval.

In the COST, participants are presented with a letter string (e.g., COFFEE) and asked to make a complex response based on four different decisions (four total button presses): lexical decision (word or nonword), syllable judgement (two syllables or not two syllables), colour discrimination (primary or secondary) and font discrimination (serif or sans serif). Decisions are made in a set sequence of key presses and the letter string remains on the screen until all four responses had been made. A 37-trial practice block of the four tasks is given before the COST.

In Savine and co-workers' (2012) study, participants were allocated to either a PM condition or a control condition. In the first Phase of the experiment (Phase 1), participants in both groups completed two COST blocks (36 trials each without PM instruction) to determine baseline COST performance. Participants were specifically instructed to make

each decision sequentially as opposed to processing all decisions at once and rapidly performing all four responses. This procedure served to better separate the processing and response of each decision during the completion of the COST. Participants received feedback across each COST trial.

In the second Phase of the experiment (Phase 2), the control group completed five COST blocks consisting of 48 trials each without PM instruction. In contrast, the PM group received detailed PM instructions where they were instructed to press the "6" key on a keyboard whenever they were presented with a target cue. Participants were informed that there were eight PM conditions in total. In the *few-attribute, specific cue* condition, the PM target was the one-two syllable word *PLANE*. In the *several-attribute, specific-cue* condition, the PM target was the non-two syllable word, *PLANE* written in red ink and in Arial font. In the *few-attribute, categorical cue* condition, the PM target was any non-two syllable word whereas in the *several attribute, categorical-cue* condition, the PM target was any two syllable word written in a primary colour and Serif font. To ensure that the PM responses had been encoded correctly, participants were asked to recite each of the PM response contingencies to the experimenter. Participants only began the COST of the second Phase when all PM response contingencies had been recited. No PM targets were presented in the first COST block but two PM targets were presented in the other four COST blocks. In each case, the PM target was the word, *PLANE* (written in red ink and in Arial font). Upon completion of the five COST blocks in the second Phase of the experiment, participants were required to verbally inform the experimenter of the PM responses contingency which was used in the task (i.e., what were the cue attributes and the appropriate response button).

The authors were able to identify the different monitoring patterns used by different people (based on the three candidate models outlined above) by calculating cost profiles based on differences in COST performance between Phase 1 and Phase 2. Cluster analysis was also performed on these data to determine whether there were objective, data-based differences in resource allocation patterns consistent with the three proposed monitoring models. Evidence for all three monitoring patterns was observed. Savine et al. (2012) found that monitoring patterns were higher for information thresholding and attentional focus relative to secondary memory retrieval. Both information thresholding and attentional focus produced high PM performance while secondary memory retrieval was associated with declines in PM performance. Ongoing task performance was only preserved in cases where information thresholding was used. Engaging in attentional focus and secondary memory

monitoring patterns produced inefficient ongoing task performance. Other factors including personality and cognitive factors influenced monitoring patterns. For example, people who scored high in openness were more likely to use information thresholding. Furthermore, higher working memory capacity was associated with better PM performance when participants were using the attentional focus monitoring pattern. Although the present study identified three key monitoring patterns used by people to aid event-based PM retrieval, there may be some situations where it might be more efficient for people to rely less on capacity-demanding processes.

Spontaneous retrieval processes (Einstein & McDaniel, 1996; McDaniel & Einstein, 2000; McDaniel et al., 2004) are fundamental in some PM situations since humans have a limited capacity for conscious control over behaviour (Bargh & Chartrand, 1999) and as such, depending entirely on capacity-demanding processes would be maladaptive (Einstein & McDaniel, 2005). This assertion is supported by self-report data that indicates that intentions spontaneously "pop" into mind during ongoing tasks (Einstein & McDaniel, 1990).

The reflexive associative theory has been proposed to explain how spontaneous retrieval might occur (Einstein & McDaniel, 1996; McDaniel & Einstein, 2000; McDaniel et al., 2004). This theory suggests that during planning, people form an association between a target cue and an intended action. Then when a target cue occurs, the intention is brought to consciousness via an automatic-associative memory system (Moscovitch, 1994) and without the need for executive resources (e.g., SAS; Shallice & Burgess, 1991). Moscovitch (1994) explains that this process is relatively automatic and occurs without the need for cognitive resources. Nonetheless, a sufficient association needs to be formed between a target cue and an intention for retrieval to occur. Following this, the target cue then needs to be processed sufficiently for accurate retrieval.

Einstein and McDaniel (1996) offer two further accounts of how spontaneous retrieval may occur for event-based prospective intentions. The simple activation model assumes that retrieval is automatic and entirely independent of "intervening controlled retrieval processes" (Einstein & McDaniel, 1996, p.125). The model assumes that when a person is given a PM task, an association is formed between the target cue and the intended action. However, as people attend to other ongoing activities, activation of this association falls to levels which are below conscious awareness. Activation levels continue to dissipate over time unless a person encounters a target cue or begins to think about the future intention.

Accordingly, when activation levels decrease, the probability of the future intention re-entering consciousness also decreases. This view is consistent with findings which show better PM performance when people are provided with specific instructions relative to general instructions about a target cue. In one study, Einstein and McDaniel (1996) asked younger and older adults to make prospective responses to either specific target cues or general target cues. In the specific target condition, participants were required to make a prospective response to a particular animal (i.e., *lion*-press a key). In the general target condition, participants were required to make a prospective response after the presentation of any animal (i.e., *animal*-press a key). Both younger and older adults made more successful prospective responses to specific target cues than they did to general target cues. The simple activation model would suggest that people form stronger cue-action pairings to specific targets than they do to general targets. If this proposal is correct, specific cue-action pairings are likely to receive greater activation compared to general cue-action pairings (see Einstein & McDaniel, 1996) which, in turn may increase the likelihood of the intended action being retrieved.

From an alternative standpoint is the Noticing and Search model (Einstein &McDaniel, 1996) which assumes that encounters with a target cue evokes feelings of familiarity, perceptual fluency, or other internal responses that allow the target cue to be noticed. Noticing a target may then initiate further probes of memory in the form of a directed search to identify the significance of the target cue. Whether or not an intention is retrieved and fulfilled is dependent on this directed search process.

Both the simple activation model (Einstein & McDaniel, 1996) and the noticing and search model (Einstein & McDaniel, 1996) emphasise the spontaneous retrieval processes associated with event-based PM retrieval. Nonetheless, it is important to note that the simple activation model views the retrieval of an intention as an entirely automatic process without the need for external resources or capacity demanding processes. If this assertion is correct and presuming that older persons are able to form the initial association (i.e., between an event-based cue and a prospective response), one would not expect to find age-related differences on event-based PM tasks. This is because the automatic retrieval processes assumed to be implicated in event-based PM tasks appear to be relatively unaffected by age (Light, 1991).

In contrast, the noticing and search model assumes that successful prospective remembering is dependent on both automatic and directed retrieval processes (Einstein & McDaniel, 1996). Since directed retrieval processes are suggested to decline with age (Light, 1991), the noticing and search model might predict that older adults will perform worse than younger adults on event-based PM tasks. Although PM has received much attention in the cognitive aging literature, there has been much debate as to whether aging induces a specific deficit in more difficult, attention demanding PM tasks or a general deficit across all aspects of PM performance. Some studies have even reported no differences between younger and older adults on event-based PM tasks (McDaniel & Einstein, 2007; Reese & Cherry, 2002). Reese and Cherry (2002) examined event-based PM performance in younger and older adults and found comparable levels of PM performance between the groups. Furthermore, there was little evidence from Reese and Cherry's (2002) study to suggest the use of strategic monitoring processes for retrieval. Both, younger and older adults made little reference (less that 5%) to thoughts about a PM intention during an ongoing task. Instead, their attention appeared to be focused primarily on ongoing task performance (69% of the time). If participants were relying on capacity demanding monitoring processes for retrieval of the intention, one would expect increased reports of conscious thoughts about the PM task. Rather, the current data suggests that both younger and older adults relied on spontaneous retrieval processes for retrieval. Similarly, McDaniel and Einstein (2007) found no evidence of age-related declines in focal PM performance. They concluded that this was because of an automatic, reflexive or obligatory retrieval of the plan upon presentation of the focal PM cue. Overall, the evidence from Reece and Cherry (2002) and McDaniel and Einstein (2007) provides support for spontaneous retrieval theories of event-based PM.

Conversely, there are a number of studies within the literature which show clear event-based PM impairment in older adults. An early investigation by Park et al. (1997) asked participants to complete a working memory task (ongoing task) and to perform an event- or time-based prospective action upon the presentation of a PM cue or after a specific time period. Age-related declines in performance were found for event-and time-based PM tasks. However, performance of the event-based PM action had a higher performance cost to the working memory task than the time-based PM tasks did. The performance cost to the ongoing task is significant as it suggests that event-based PM loads heavily on attention demanding processes which detract from performance on ongoing tasks. More recent data suggests that older adults are impaired on event-based PM tasks which are conducted in the

laboratory (Kvavilashvili, Cockburn and Kornbrot, 2013) and in more naturalistic settings (Shum, Levin & Chan, 2011). Kliegel et al. (2001) argue that event-based PM impairments in older adults are underpinned by deficits in planning, initiation and execution stages of event-based PM tasks (Kliegel et al., 2001). Indeed, event-based PM performance is improved when older adults are given additional planning time prior to the completion of a PM task (Shum, Cahill, Hohaus, O'Gorman & Chan, 2013). Overall, these findings are consistent with the noticing and search model and indicate that some event-based PM tasks may require the use of strategic monitoring processes for accurate retrieval.

In conjunction with the inconclusive findings in relation to event-based PM retrieval and aging, McDaniel and Einstein (2000) argue that it is adaptive for people to have a flexible system where intentions can be retrieved through several mechanisms. The multiprocess theory (McDaniel & Einstein, 2000) assumes that retrieval can occur through monitoring and/or spontaneous retrieval processes. However, the processing method used for retrieval depends on several factors including the nature of the PM task (important vs. unimportant), the target event and the ongoing task. If this assertion is true, it may help to explain the inconclusive findings regarding the effects of aging on event-based PM.

One dimension of the multiprocess theory refers to the association between a target and an intended action. Specifically, improved PM performance has been found under conditions where there is a strong association between a PM cue and an intended action (McDaniel et al., 2004). This is because PM cues which are highly associated with an intention involve automatic retrieval processes (McDaniel, Robinson-Reigler & Einstein, 1998). For example, in the case of buying some fruit when passing the grocery store, the target (grocery story) typically has a common association with the intended action (buying fruit). Conversely, less highly associated target-intended action pairings may be formed if one had to buy a CD from the grocery store. This is because the target (grocery store) may not normally be associated with the intended action (buying a CD). In relation to this, McDaniel and Einstein (2000) argue that when a highly associated target-intended action pairing has been formed, the presence of a target event is likely to elicit automatic (spontaneous) retrieval of an intended action. On the other hand, poorly associated target-intended action pairings are likely to require more refined monitoring processes for retrieval (McDaniel & Einstein, 2000).

The multiprocess theory also highlights the importance of focal and non-focal processing of the target event in the retrieval of an intention. In terms of cue focality, PM target cues are suggested to be more focal when the ongoing task involves processing the defining features of the PM targets compared to when ongoing task processing is more peripheral (Rose, Rendell, McDaniel, Aberle & Kliegel. 2010). Thus, for focal PM tasks, PM targets are processed in a manner which will allow spontaneous retrieval of an intended action. An everyday example of focal processing may include remembering to return a borrowed DVD to a friend. In this example, the intention may not be fulfilled until a person next decides to watch a film. In this case, the multiprocess theory would suggest that when the DVD's become a focus of the ongoing task (choosing a DVD to watch), an automatic retrieval process is elicited which reminds a person of the previously formed intention (to return the borrowed DVD to a friend).

On the other hand, if an ongoing task involves non-focal processing of a target (a target is encountered but is not a part of the stimuli processed in the ongoing task, i.e., if a person decides to go out for a meal rather than watching a DVD, the DVD's are unlikely to receive focal processing), strategic monitoring might be needed to ensure that attention is diverted from the ongoing task and towards the non-focal target (McDaniel & Einstein, 2000). Furthermore, non-focal PM cues which demand significant strategic and monitoring resources produce more consistent declines in longer delay conditions compared to focal PM cues (Einstein et al., 2005).

Considering the particular cognitive processes which underpin focal and non-focal PM tasks, one may expect older adults to perform worse on non-focal PM tasks compared to focal PM tasks. This is because older adults are impaired in strategic, effortful processes and less so in automatic cognitive processes (Kliegel et al., 2008). Findings which suggest that age-related differences are more pronounced when targets are non-focal to the ongoing task compared to when targets are focal to the ongoing task support this proposal (Rendell & Craik, 2000; Rendell, McDaniel, Forbes & Einstein, 2007). With relatively few researchers distinguishing between the use of either focal or non-focal PM tasks in their studies, Kliegel and colleagues' (2008) attempted to quantitatively analyse all available literature on age-related differences in event-based PM. PM tasks from each study were distinguished according to their use of either focal or non-focal PM cues. Overall data from 4709 participants provided clear evidence for age-related declines in non-focal PM tasks relative to focal PM tasks. Given that non-focal PM tasks load heavily on effortful attentional processes

and processing resources are suggested to decline with age (Craik, 1986), these findings provide substantial support for the role of monitoring in the processing of non-focal target cues and the involvement of automatic retrieval in the processing of focal target cues.

The multiprocess theory was explored thoroughly in Einstein et al's (2005) five-study investigation. Einstein et al's (2005) research was similar to an approach adopted by Smith (2003) and evaluated the costs of performing a PM task on the speed and accuracy of performing non-target ongoing task items. If the completion of a PM task is shown to increase the time taken to perform an ongoing task (for non-target items), then this is suggested to reflect the use of monitoring processes for retrieval. In contrast, spontaneous retrieval processes are thought to be implicated in cases where no performance costs are observed.

Einstein et al's (2005) first experiment involved an ongoing task whereby participants were presented with a single word with a category heading and asked to decide whether the single word was a member of the category or not. There were two experimental conditions. Focal processing conditions required participants to press a key (i.e., the prospective response) after being presented with a target word (e.g., tortoise) whereas non-focal processing conditions required participants to press a key whenever a target syllable (e.g., tor) was presented. By way of testing the effect of task importance on PM performance, Einstein et al. (2005) also manipulated the degree to which each PM task was emphasised during task instruction. Significant performance costs to the ongoing task were observed in conditions which involved non-focal processing of a target. It is likely that this performance cost can be accounted for by the use of strategic monitoring processes where a person searches the environment for non-focal targets. It is noteworthy that no significant performance costs were found in conditions which involved focal processing of the target. As assumed by the multiprocess theory, PM tasks which involved focal processing of a target relied primarily on the use of spontaneous retrieval strategies. Furthermore, PM performance remained high under the focal processing condition suggesting that monitoring is not always essential for accurate PM retrieval. In addition, higher performance costs to the ongoing task were found when PM tasks had been highly emphasised in the task instructions. It is assumed that high emphasis instructions led to greater monitoring which in turn may have compromised performance costs to the ongoing task. Critically, however, compromised performance was only apparent in non-focal conditions. Einstein et al. (2005) explain that the

spontaneous retrieval processes associated with focal processing of targets is sufficient enough to allow for accurate retrieval. Thus, the completion of focal PM tasks does not impair ongoing task performance as there is little need for the use of resource demanding monitoring processes.

The aforementioned findings were replicated in Einstein et al's (2005) second experiment. That is, the nature of the target event (focal vs. non-focal) was an accurate predictor of the process employed for retrieval. In contrast to Study 1 where task importance was manipulated, all participants in Study 2 received moderate emphasis instructions relating to the PM tasks. Furthermore, the presentation of the word-pairs was counterbalanced such that the authors were able to evaluate performance across the experiment without the possible limitation of item effects. Experiment 2 showed that monitoring processes declined across trials in the non-focal target condition. This finding is in line with the assumption that monitoring is a controlled process (Smith, 2003) and that people have a limited capacity for controlled processing (Bargh & Chartrand, 1999). Furthermore, decreased monitoring in the non-focal condition was associated with PM performance decrements. Importantly, this effect was not found in the focal condition further evidencing the use of spontaneous retrieval strategies in PM tasks which involve the focal processing of a target.

Einstein et al's (2005) third experiment attempted to test an alternative perspective that performance costs can be found in focal conditions with more complex PM demands, as proposed by Smith, (2003). Einstein et al. (2005) compared performance costs on an ongoing task were compared with either one or six target events. The findings showed that performing a PM task with one focal-target event did not induce performance costs on an ongoing task. Conversely, for PM tasks with six focal-target events, performance of the PM tasks did produce a significant performance cost in the accuracy and speed of performing the ongoing task. This finding supports Smith's (2003) proposal that PM task demands can mediate the strategies used for retrieval. Where participants were asked to respond to a number of PM targets as opposed to a single PM target, it would appear that they were using monitoring strategies for retrieval albeit at the expense of processing of the ongoing task.

Einstein et al's (2005) fourth experiment explored the individual differences underlying different PM processes. Experiment 4 identified the potential use of both spontaneous retrieval processes and monitoring processes in PM situations. Importantly, some participants were shown to use monitoring processes in conditions which are suggested

to encourage spontaneous retrieval processes (focal PM tasks). Furthermore PM differences were not observed between participants who used spontaneous retrieval processes or monitoring processes. Overall, these findings confirm assumptions of monitoring theory that people rely on multiple retrieval processes in different PM situations.

One of the main characteristics of spontaneous retrieval processes is that they should occur without intention (Einstein et al., 2005). With this in mind, experiment 5 aimed to explicitly test the existence of spontaneous retrieval processes by investigating whether there was any evidence of PM retrieval in situations where participants were instructed to ignore a PM intention. This was done by giving participants a PM instruction and asking them complete a lexical decision task with no PM intention and an ongoing task where the PM intention had to be retrieved. In the lexical decision task, participants were instructed to ignore the PM task and to simply respond as quickly as possible. Thus, there was no requirement for the PM intention to be fulfilled during the lexical decision task and as such there should have been no monitoring of the items for the PM target. According to the spontaneous retrieval view, the presentation of a PM cue even in cases when no PM intention is required (i.e., in the lexical decision task) should trigger retrieval processes which slow down the making of a lexical decision. In addition, the instruction to disregard the PM task was included to discourage the use of monitoring processes for retrieval. Despite being instructed to ignore PM targets, participants were slower to respond to PM targets compared to non-PM targets in the lexical decision task. This finding confirms the use of spontaneous retrieval processes in PM situations.

Overall, the findings from Einstein and colleagues' (2005) five study investigation support the multiprocess theory. First, the findings provide significant evidence for the existence of spontaneous retrieval processes and highlight their utility in supporting good PM. Furthermore, it appears that people rely on different retrieval strategies (i.e., monitoring or spontaneous retrieval processes) according to the demands of PM situations. In situations that require the focal processing of a target event, people are more likely to use spontaneous retrieval processes. On the other hand, monitoring processes are suggested to be implicated when PM tasks involve the non-focal processing of a target event.

More recent data from McBride and Abney (2012) further supports the multiprocess view of PM. By comparing PM task accuracy and ongoing task completion speed in baseline and different PM conditions (focal and non-focal), McBride and Abney (2012) found that PM

task completion rates were higher for focal PM task conditions relative to non-focal PM task conditions. According to assumptions of the multiprocess view, it is likely that focal PM targets are processed in a manner which allows for spontaneous retrieval of an intended action. In comparison, non-focal PM targets require attention demanding resources and strategic monitoring processes. It is therefore possible that the specific monitoring patterns that were used by participants in the non-focal PM task conditions compromised PM performance. According to Savine et al. (2012), the PM deficits observed on non-focal PM task conditions are likely to be a result of the use of secondary memory retrieval monitoring patterns. Secondary memory retrieval is a monitoring pattern where people formulate a general memory trace of an intended action and consistently shift attention from an ongoing task to active attempts of retrieval of specific details of the PM intention. However, adopting this detailed monitoring process has been associated with declines in PM performance (Savine et al., 2012).

2.3.3.2 Time-based Prospective Memory

Intentions whereby the execution of an action is governed by the passage of time rather than by the presence of an external cue or event are called time-based PM tasks (Einstein & McDaniel, 1990). Intentions that need to be performed at a specific time or after a predefined period of time have elapsed both fall under this term. Typical time-based PM tasks might include remembering to attend an appointment at a specific time (e.g., 10am) or remembering to take the dinner from the oven after a cooking period has elapsed (e.g., after 20-minutes has passed). In each case, the realisation of an intention is dependent on the strategic monitoring of time. Laboratory tasks which are commonly used to investigate time-based PM involve remembering to mail items to an experimenter on a specific date (see Dobbs & Rule, 1987; Meacham & Leiman, 1982) or remembering to complete a questionnaire at various time-intervals during the test-session (Hadjiefthvoulou et al., 2011a; for further details see Chapter 5, Section 5.2).

The estimation of time during time-based PM tasks is known as prospective timing. Conclusions from a recent meta-analytic review (Block, Hancock & Zackay, 2010) suggests that prospective timing is dependent on an attentionally driven internal clock mechanism and not by memory for interval information (i.e., the information required to be remembered during a specific time-interval). To test this proposal, Waldum and Sahakyan (2012) gave

participants an ongoing task with a time-based PM element and asked them to produce an estimation of time after the entire time interval (Experiment 1). During the time interval, participants were required to complete a lexical decision task (ongoing task) while a number of songs were played in the background. Longer verbal time estimates were produced when participants remembered more songs from the time interval. This finding is not in concert with conclusions from Block et al. (2010) and rather suggests that prospective timing is affected by memory for interval information. One possible implication of this finding might be that people who display accuracy in terms of prospective timing do so at the expense of memory for interval information. Furthermore, this finding implies that people who remember to carry out PM tasks may do so at the expense of other ongoing everyday activities.

Early investigations of time-based PM have explored the strategies employed by people to aid prospective remembering and indeed prospective timing (Ceci & Bronfenbrenner, 1985; Harris & Wilkins, 1982). One of the first strategies to be explicitly identified in the literature is strategic time monitoring. Strategic time monitoring can be characterised by the following three phases; a) *an early calibration phase* where people engage in frequent clock-monitoring in an attempt to synchronise their own psychological clocks, b) *an intermediate phase* where clock-monitoring is less frequent and the person concentrates on other activities, c) *a scalloping phase* where a period of intense clock-checking occurs a short time before the delayed intention has to be realised (Ceci & Bronfenbrenner, 1985). Consistent with this proposal, Harris and Wilkins (1982) found that their sample of adult women engaged in frequent clock-checking behaviour shortly after being asked to complete a time-based PM task**.** This was followed by a period of less frequent clock-checking where the women were able to focus on other ongoing tasks. Finally, there was a strategic burst of clock-monitoring just before the delayed intention should have been realised. Importantly, time-based prospective remembering was enhanced when participants intensified their clock-monitoring behaviour towards the end of the target period.

A further study of a younger sample of 10 and 14 year old children showed similar findings (Ceci & Bronfenbrenner, 1985). Children were given the task of removing cupcakes from an oven following a 30-minute time-delay. There were two experimental conditions whereby participants either completed the task in a familiar (i.e., their own home) or an unfamiliar context (i.e., a laboratory). A clock was provided for time monitoring and children were given the opportunity to play a video game during the delay interval. Total number of

clock checks did not predict time-based PM performance. Rather, increased clock-monitoring towards the end of the baking period increased prospective remembering suggesting that this may also have increased accuracy in prospective timing. Age-related differences in time-based prospective remembering were also found. Specifically, older children (14 year olds) made more efficient use of strategic time monitoring, especially towards the end of the baking period This particular study has highlighted improved PM performance as children become young adults. However PM performance does not remain stable throughout adulthood with a growing body of literature suggesting PM performance becomes impaired in older adults.

Theoretical Models of time-based PM

An important characteristic of prospective remembering is that the recollection of an intention occurs without an explicit request for retrieval. Below several theories which attempt to explain how people might retrieve time-based intentions from memory are outlined.

Harris and Wilkins' (1982) model of time-based PM (Test-Wait-Test-Exit; TWTE model) suggests that a PM task is encoded and a test of memory is conducted after a period of time has elapsed. If the time for retrieval is not correct, further tests of memory are conducted until a test is performed during a critical period (i.e., the time when it is appropriate for an intention to be realised). It is at this point when a person should then perform an action directed towards the realisation of an intention. This model of time-based PM assumes that the monitoring of time leads to better PM performance. Studies which have shown evidence of strategic time monitoring during time-based PM tasks and in particular during the period preceding the target time support the TWTE model (Einstein & McDaniel, 1990; Harris & Wilkins, 1982). While it is assumed that monitoring is a deliberate and self-initiated process which is reliant upon a person's attentional resources (Einstein et al., 1995; Park et al., 1997), the TWTE model fails to explain how a person makes themselves aware of time in the absence of cues (Sellen, Louie, Harris & Wilkins, 1997, p.484). Harris and Wilkins (1982) suggest that an intention might spontaneously appear in a person's mind for no apparent reason. Findings which have presented self-report accounts of spontaneous recollections for real-life intentions support this possibility (Ellis & Nimmo-Smith, 1993).

Alternatively, Wilkins and Baddeley's (1978) "Random Walk" model suggests that time-based PM retrieval is dependent entirely on incidental factors rather than self-initiated processes. The "Random Walk" model is based on the concept that the mind is a multidimensional space. They suggest that a trace which represents the intention is placed in this space when it is first formulated. However, during the time interval between the formation of an intention and its retrieval from memory, a person's thoughts are displaced throughout this space. The areas in which a person's thoughts become distributed are dependent upon the stimuli in the environment and the activities that they engage in during the time interval. The likelihood that an intention will be realised is increased if a person's thoughts are located around the trace for an intention at the appropriate time for retrieval.

In a recent investigation, Kvavilashvili and Fisher (2007) examined the extent to which the TWTE model and The "Random Walk" model can explain the retrieval processes involved in event- and time-based PM. The authors compared self-reported rehearsal processes involved in time- (Study 1 and Study 2) and event-based (Study 3) PM tasks. Participants were required to phone the experimenter at a specific time (time-based PM) or after they received a text message (event-based PM). In order to identify the underlying retrieval processes involved in PM retrieval, participants were asked to keep a record of the occasions on which they thought about an intention during a seven day time interval. Findings confirmed assumptions of the TWTE model (Harris & Wilkins, 1982) and showed that time-based intentions were either triggered by incidental cues or appeared in a person's mind for no obvious reason. Despite these findings, there were a few reports of self-initiated rehearsals where participants used effortful retrieval processes to aid remembering for time-based intentions.

In addition to this, Kvavilashvili and Fisher (2007) suggest that the delay period between the formation of an intention and its retrieval from memory (retention phase) can influence the retrieval process. First, they propose that a person will keep short-term intentions in their mind for the entire delay period (i.e., conscious thoughts about the intention). This suggestion is in line with Harris and Wilkins' TWTE model (1982) in that it assumes that time-based PM tasks involve self-initiated retrieval processes. However, the process of retrieval for long-term PM tasks appears to be very different. This is because there is additional opportunity for the intention memory to dissipate over longer delay periods. Reports from participants in Kvavilashvili and Fisher's (2007) investigation showed low

levels of self-initiated rehearsal in long-term PM tasks. Instead, there were increased incidences of rehearsals which were triggered by incidental cues completely unrelated to the intention. Once again, this finding is consistent with assumptions of Harris and Wilkins (1982). Further evidence for this model of time-based PM comes from findings which suggest that people use incidental cues including clocks, calendars and timetables to aid time-based PM (Harris & Wilkins, 1982; Sellen et al., 1997).

While Kvavilashvili and Fisher's (2007) investigation provides substantial support for Harris and Wilkins' TWTE model (1982) of time-based PM, some other important conclusions must be acknowledged. The overall findings suggest that time- and event-based PM are not mediated by different retrieval processes and that thoughts about each type of intention (event- or time-based) occur through one or a combination of the following routes. Rehearsals are either prompted by incidental cues, by self-initiated planning processes, or by no apparent triggers. In relation to this finding, it seems that the difference between the retrieval processes for time- and event-based PM is quantitative rather than qualitative. For example, the low activation levels of event-based PM tasks appear to be constant, yet sufficient to sensitise a person towards a target. Nonetheless, this level of activation may not be enough for the task to pop into one's mind. In contrast, the activation levels of time-based tasks appear to be higher and fluctuate over time resulting in episodic conscious thoughts about the task.

2.4 Age-related deficits in prospective memory

According to Einstein and McDaniel (1999), there are a number of cognitive processes which are more susceptible to the effects of aging than others. For example, aging may have detrimental effects to memory tasks that require self-initiated retrieval processes (Craik, 1986). If this proposal is true, one would expect older adults to perform worse than younger adults on memory tasks with little external support from the environment for retrieval. This assumption is consistent with findings which show higher age-related decrements on free recall tasks compared to recognition based tasks (Craik, 1986; Craik & McDowd, 1987). Considering that free recall tasks involve some instruction for a memory search by an experimenter and PM is dependent on the ability to remember, an age-related decrement in PM performance might also be expected (Craik, 1986).

As previously noted, a number of studies have found age-related impairments in event-based PM performance (Kvavilashvili et al., 2012; Park et al., 2007; Shum et al., 2013)

whilst others have not (McDaniel & Einstein, 1996; McDaniel & Einstein, 2007; Reese & Cherry, 2002). The differences between these findings might be explained by differences in the processing of PM target cues across studies. To demonstrate, there is considerable evidence to suggest that older adults display impairment on PM tasks with non-focal PM targets but not on PM tasks with focal PM targets (Rendell & Craik, 2000; see Kliegel et al., 2008). This is because non-focal PM tasks are dependent on the use of self-initiated monitoring strategies which are known to be impaired in older adults (Kliegel et al., 2008).

Moreover, event- and time-based PM tasks do not involve the same self-initiated or attention demanding processes (Einstein & McDaniel, 1990). For example, in event-based PM tasks, a memory for an intention is externally cued by some aspect of the environment (e.g., a person, an object, etc.). By way of contrast, time-based PM tasks require the use of self-initiated retrieval strategies (see Ceci & Bronfenbrenner, 1985; Harris & Wilkins, 1982). As a result event- and time-based PM may be differentially affected by aging. Support for this proposal has emerged from studies which have shown age-related decrements in time- but not in event-based PM performance (Bastin & Meulemans, 2002; Einstein et al., 1995; Katai, Maruyama, Hashimoto, & Ikeda, 2003; Kliegel et al., 2001; Khan, Sharma & Dixit, 2008).

Findings from a meta-analytic review by Henry, MacLeod, Phillips and Crawford. (2004) suggest that older adults perform worse than younger adults on event-based PM tasks which load heavily on controlled strategic processes (see meta-analytic review by Henry et al., 2004). Henry et al. (2004) also argue that age-related declines in PM are smaller for PM tasks which involve relatively automatic processes (focal event-based PM tasks) and larger for PM tasks which involve relatively effortful processes (non-focal PM tasks or time-based PM tasks). Despite these conclusions, a more recent meta-analysis (Uttl, 2008) has criticised Henry et al's (2004) conclusions on the basis that they failed to account for prevalent ceiling effects which ultimately reduce the effects sizes reported in their meta-analysis. That is, there is no difference between younger and older adults on easy PM tasks since both groups achieve perfect or near perfect scores. In contrast, there is a large age-related decline in performance on more difficult PM tasks.

A summary of Uttl's (2008) meta-analysis indicates that while event-based PM proper and vigilance/monitoring decline with aging, the decline is much larger in the latter. In furthering the current understanding of age-related declines in PM, Uttl (2008) suggests that

the decline is relatively small until a person is in their 50's or 60's but accelerates thereafter. Importantly, Uttl's (2008) meta-analysis provides no indication that aging may spare any particular aspect of PM performance. That is, event- and time-based PM performance decline with age. They argue that previous claims of no age-related declines in PM performance (McDaniel & Einstein, 1996; McDaniel & Einstein, 2007; Reese & Cherry, 2002) are likely to be related to methodological and conceptual issues including age confounds, ceiling affects and lower statistical power.

Acknowledgement of the aforementioned cognitive aging literature is highly relevant to the current project since illicit drug users exhibit similar kinds of executive function deficits as are found in older persons. Specifically, older adults (Herman, Mirelman, Gilardi & Schweiger, 2010; Prakash et al., 2009) and drug users (Gouzoulis-Mayfrank et al., 2000; Gouzoulis-Mayfrank & Daumann, 2009; Zakzanis, Campbell, & Jovanovski, 2007) demonstrate impairment in executive functions which are regulated by the frontal lobes. This is significant since PM performance is also mediated by areas of the prefrontal cortex (Cheng et al., 2008; Okuda et al., 2007) and as such, PM impairment in older persons might be suggestive of the possibility of PM deficits in illicit drug users.

2.5 Strategies used for remembering

PM performance can be influenced by the strength of an association between a PM cue and an intended action (see *section* 2.3.3.1). However, the impact that a strong cue-action association can have on PM performance is also believed to underpin the effectiveness of an important retrieval strategy (McFarland & Glisky, 2012). Gollwitzer (1999) developed a technique to improve PM by integrating two fundamental components of delayed intentions; the situation (i.e., the retrieval context) which provides an opportunity for a person to execute an intention (*where* and *when* an intention should be retrieved) and the intended action (*what* it is that has to be done). This combination of information allows people to form a verbal commitment or an association in the structure of "if X occurs, then I will do Y". Gollwitzer called these verbal commitments, *implementation intentions* and there is a substantial amount of research which suggests that this technique is an effective means of fulfilling delayed intentions (Chasteen, Park & Shwarz, 2001; Cohen & Gollwitzer, 2006; Kardiasmenos, Clawson, Wilken & Wallin, 2008; Schnitzspahn & Kliegel, 2009).

Further research has explored the extent to which the use of imagery techniques can improve prospective remembering. To demonstrate, in normal event-based PM tasks, participants are asked to respond to an environmental cue during the completion of an ongoing task. By using imagery techniques, participants are able to visualise themselves witnessing and responding to PM related stimuli during an ongoing task (e.g., responding to an animal word (PM cue) during a lexical decision task) (Brewer, Knight, Thadeus meeks & Marsh, 2011). Of the few studies that have investigated the effects of imagery techniques on PM performance, overall findings have been relatively inconclusive. Guynn, McDaniel and Einstein (1998) found that participants who were asked to visualise PM cues in the context of their occurrence (i.e., imagine the PM cue appearing in an ongoing task) performed similarly to participants who were given standard instructions (no instruction to visualise the PM cue). Similarly, McDaniel et al. (2008) failed to find any effect of imagery instruction on PM performance. In contrast to these findings, other studies have reported improved PM performance when participants are explicitly instructed to imagine the presentation of the PM cue during an ongoing task (Brewer et al., 2011; Meeks & Marsh, 2010; Paraskevaides et al., 2010). Brewer and colleagues (2011) explain that imagery fosters a cue-to-context association and in doing so, reduces interference to irrelevant information in the ongoing task (i.e., lures). In addition, imagining may increase PM performance by increasing the salience of PM cues so that they are detected more easily when they are presented (Paraskevaides et al., 2010).

An alternative explanation suggests that PM performance is enhanced because participants rely on episodic memory to imagine future contexts (Brewer & Marsh, 2010). Findings from Brewer and Marsh (2010) have shown increased prospective remembering when participants are provided with additional episodic information about the context in which PM cues will occur before encoding. Brewer and Marsh (2010) suggest that the additional episodic information about the context in which PM cues will later appear allows participants to encode a more detailed representation of their future context. Conclusions from this particular study suggest that the extent to which PM performance is improved by the use of imagery is highly dependent on episodic memory simulation. If this is the case, this concept may explain why some studies have failed to report positive effects of imagery on prospective remembering (McDaniel et al., 2008). That is, participants may have failed to produce detailed cue-to-context representations due to a lack of episodic information relating to the PM cue and its future context before encoding.

Forming strong cue-to-context representations can have several consequences to processing in the ongoing task (Brewer et al., 2010). First, following a strengthened association between PM cues and future context where they are expected to occur, the encoded intention becomes almost immediately active when the appropriate context arises. Ultimately, this is proposed to lead to higher levels of PM performance (see also Marsh, Hicks & Cook, 2006). Second, in cases where the context is a critical component of the encoded intention (e.g., during the COST where the PM response involves pressing a particular key whenever you see the word, *PLANE* written in red ink and in Arial font), the use of imagery techniques allows for people to verify that the PM cue is present and in the correct context. In this situation, the PM response should not be executed unless the PM target (i.e., *PLANE*) is presented in the correct context (i.e., it must be written in red ink and in Arial font). Third, information that is not related to the intention but occurs in the correct context is recognised and subsequently rejected provided that a strong cue-to-context association has been formed.

Given that implementation intentions and imagery techniques have both been shown to have positive effects on prospective remembering, research has begun to investigate whether or not the combined use of both strategies can improve PM performance beyond the use of either strategy alone. Once again, the findings surrounding this proposal have been inconclusive. McDaniel et al. (2008) found that imagery instruction which included a verbal "if...then" commitment (combined imagery and implementation intention group) enhanced PM performance. However, no difference in PM performance was found between participants who were provided with imagery instruction alone and participants were provided with standard instructions (i.e., no explicit instruction to visualise). Overall, these findings appear to indicate that the verbal commitment (implementation intention) was the vital component of the combined imagery and implementation intention group which improved PM performance.

In a more recent study, McFarland and Glisky (2011) divided a sample of 64 undergraduate students into one of four instructional conditions (read only, implementation intention only, imagery only, combined implementation intention and imagery). Performance on a laboratory based PM task was measured. Participants in the implementation intention only, imagery only and the combined implementation intention and imagery groups all performed significantly better than participants in the read-only group. However, there was

no difference in PM performance between the three other instructional groups. Thus, there does not appear to be any additional benefit to PM performance when implementation intention and imagery techniques are used together compared to when either strategy is used alone. This finding supports Cohen and Gollwitzer's (2008) suggestion that imagery is not a vital component of implementation intentions.

Other strategies that have been linked to improved remembering include metacognitive factors. More specifically, making performance predictions (i.e. metacognition) has been shown to increase performance on RM tasks (Spellman & Bjork, 1992). Given that RM has been associated with PM performance; it is plausible that PM may also be affected by metacognitive factors. Only a few studies have directly investigated the effects of metacognition on PM (Devolder, Brigham, & Pressley, 1990; Knight, Harnett, & Titov, 2005; Meeks, Hicks, & Marsh, 2007). However, the research that is available suggests that people with higher general memory *self-efficacy* (beliefs about one's own memory abilities) perform better in laboratory-based PM tasks compared to participants with lower memory self-efficacy (McDonald-Miszczak, Gould, & Tychynski, 1999; Zeintl, Kliegel, Rast, & Zimprich, 2006).

In another study, Meeks et al. (2007) asked participants to complete a lexical decision task (i.e., an ongoing task) and to make a PM response following the presentation of an animal word (animal condition) or a word containing the syllable *tor* (syllable condition). Overall, participants were shown to underestimate PM performance and these findings are consistent with those from another study in the literature (Knight et al., 2005). Further findings showed that performance predictions were positive correlated with overall success in the animal condition. Although findings from Meeks et al. (2007) suggest that people are aware of their PM ability, the findings have been criticised on methodological grounds. For example, performance predictions were made in reference to overall PM performance (animal condition & syllable condition combined) which may have resulted in inaccurate and vague performance predictions (Meier, von Wartburg, Matter, Rothen, & Reber, 2011). For example, in cases where participants reported confidence in their ability to perform PM tasks, it is unclear as to whether they were particularly confident in one particular condition or both conditions.

Knight et al. (2005) controlled for this factor by asking participants to provide a performance prediction for every PM cue in a PM task. Knight and colleagues investigated differences in predicted PM performance and actual PM performance between a group of traumatic brain injury (TBI) patients and healthy controls. Participants watched a video where they took the role of a person driving and walking through a city. Participants were required to remember to execute several PM tasks (e.g., buy bread) when presented with one of 20 PM cues (e.g., bakery). Using a 4-point scale, participants were asked to indicate how likely they thought they were to execute each specific PM task. Patients overestimated their PM performance while the control group underestimated their PM performance. Correlational analyses revealed that both groups had metacognitive awareness of their PM performance.

A recent study by Meier et al. (2011) attempted to explore the extent to which making a PM performance prediction can enhance prospective remembering. One-hundred and forty undergraduate students performed a complex short-term memory task with a PM element. Half of the participants were then asked to give performance predictions prior to performing a PM task. The specificity of the PM task was also manipulated. Participants were either instructed to make a prospective response to the presentation of a word that is a musical instrument (categorical condition) or to respond to the word “trumpet” (specific condition). Performance predictions improved PM performance for the categorical condition only.

Several explanations have been put forward for this finding. First, Meier et al. (2011) suggest that simply thinking about carrying out a future intention leads to a more realistic opinion about task difficulty. This then results in the use of more efficient retrieval strategies which in turn enhance PM performance. Second, Meier and colleagues (2011) propose that making performance predictions strengthens the association between the PM cue and the retrieval context (information relating to where and when an intention should be retrieved). Thus, when a PM cue is encountered in the correct context, the PM intention is likely to be retrieved. Third, Meier et al. (2011) argue that making performance predictions may alter the dynamics of the PM tasks. For example, making a performance prediction might increase participants’ commitment and/or motivation towards the PM task. The resultant increase in commitment and/or motivation may accentuate perceived task importance (see Meier et al., 2011). This is noteworthy considering that higher perceived task importance has been linked to increased PM performance (Kliegel et al., 2004)

Further evidence from Meier et al's (2011) study showed that cue specificity (categorical or specific) had a significant effect on retrieval experience. Specific PM instructions (i.e., respond to the word "trumpet") encouraged the use of spontaneous retrieval strategies. Although speculative, it is likely that participants in the specific PM instruction condition formed specific cue-action pairings whereas participants in the categorical PM instruction condition formed more general cue-action pairings. Einstein and McDaniel (1996) propose that specific cue-action pairings receive greater activation compared to general cue-action pairings. Increased activation resulting from the formation of specific cue-action pairings increases the likelihood of the intended action being retrieved when the PM cue is presented. Importantly, PM cues which are highly associated with an intention are suggested to involve automatic retrieval processes (McDaniel et al., 1998).

2.6 Chapter summary

There are a number of different classifications of PM which can be identified according to different phases of information processing (encoding, retention, retrieval and performance; Kvavilashvili & Ellis, 1996). With regard to the encoding phase, PM tasks can be distinguished according to the perceived importance of the delayed intention (important and unimportant intentions), the decisions which operate prior to the formation of an intention (intentions based on simple or difficult decisions) and whether the intention has been formed by oneself or another person (self or other generated intentions).

Further, PM intentions can be characterised by the length of the interval between the formation of an intention and the time when an intention should be retrieved from memory (the retention phase; short- and long-term PM tasks). Overall evidence within the literature indicates that PM performance decreases as the retention interval is increased (Brandimonte & Passolunghi, 1994; McBride et al., 2011; Meier, Doerfler, Hawes, Hicklin, & Rocha, 2006). This is because delayed intentions with longer delay intervals require extended periods of conscious awareness compared delayed intentions with shorter delay intervals (Einstein & McDaniel, 1990; Kvavilashvili & Fisher, 2007). In addition, there is increased opportunity for a delayed intention to dissipate over time during longer delay intervals. As such, there is additional need for the use of monitoring strategies in long-term PM tasks. Given that monitoring processes decline over extended delay periods (Einstein et al., 2005; Loft et al., 2008), it is perhaps unsurprising that there is a decline in PM performance for longer delay

intervals. This effect is particularly evident for non-focal PM tasks which require self-initiated monitoring processes for retrieval (McBride et al., 2011).

In addition, PM tasks can be identified according to whether they are governed by an external episode (i.e., a person, object or location) or by the passage of time where there is no explicit request for retrieval. These are termed event- and time-based PM tasks respectively. Overall, event- and time-based PM tasks share the same retrieval characteristics in that they both require some degree of self-initiated and/or automatic retrieval processes (Harris & Wilkins, 1982; Kvavilashvili & Fisher, 2007; Wilkins & Baddeley, 1978). However, the extent to which these retrieval processes are employed is dependent on other features of the PM task including whether the PM target cue is focal or non-focal to the ongoing task and whether there is short or long delay between the formation of an intention and its retrieval from memory (Einstein et al., 2005; Kvavilashvili & Fisher, 2007). The use of monitoring strategies are increased in event-based PM tasks when the PM target cue is non-focal to the ongoing task compared to when the PM target is focal to the ongoing task (McBride & Abney, 2012). Monitoring strategies are also more likely to be used for more complex event-based PM tasks (non-focal PM tasks, Einstein et al., 2005; Smith, 2003) and time-based PM tasks which have extended delay intervals (Kvavilashvili & Fisher, 2007). Overall, it appears that event- and time- based PM tasks do not differ in terms of specific retrieval processes but rather can be separated according to the quantitative involvement of rehearsal, self-initiated planning or spontaneous triggers (Kvavilashvili & Fisher, 2007).

Chapter 3: The neuropsychology of prospective memory

Chapter Outline

PM is a complex memory process which involves several components including the planning of an intention, the retrieval of an intention at an appropriate time, and the execution of an intended action (Dobbs & Reeves, 1996). Consequently, it is likely that the processes employed by each component rely on different parts of the neural system. Amongst a body of existing literature, there is a general consensus for PM's dependence on medial temporal hippocampal processes, areas of the prefrontal cortex (PFC), and different areas within these regions (West, 2005). The current Chapter examines how the aforementioned brain regions are differentially challenged by event- and time-based PM situations.

3.1 Neuropsychology of event-based prospective memory

As previously discussed, event-based PM retrieval can be supported by the use of monitoring and/or spontaneous retrieval processes (McDaniel & Einstein, 2000). However, each retrieval method appears to challenge different aspects of the neural system. For example, there is a general consensus that monitoring processes are supported by frontal regions (Burgess, Scott & Frith, 2003; Reynolds, West & Braver, 2009). As a result, McDaniel and Einstein (2011) argue that non-focal processing of targets in event-based PM tasks (where there is thought to be a need for monitoring processes; see Rendell & Craik, 2000; Rendell, McDaniel, Forbes & Einstein, 2007) depend significantly on frontal processes (McDaniel & Einstein, 2011). Alternatively, spontaneous retrieval processes are thought to mediate a reflexive associative system (see McDaniel & Einstein, 2000) which places significant demand on medial temporal structures including the hippocampus (Moscovitch, 1994). The paragraphs below outline recent neuroimaging work that has attempted to determine the role of neuropsychological process in event- (focal and non-focal) and time-based PM tasks.

Neuropsychology of non-focal (event-based) Prospective Memory tasks

In a neuroimaging study, Burgess et al. (2003) employed PET and examined changes in regional cerebral blood flow (rCBF) across four experimental conditions. rCBF was examined in a baseline condition, an ongoing task only condition, an ongoing task plus a delayed intention condition (unpracticed) and an ongoing task plus a delayed intention condition (practiced). A number of ongoing tasks were used which each involved the

presentation of different stimuli types. In a number condition, participants were presented with a pair of numbers and asked to identify whether the highest number was on the left- or right-hand side of the computer screen. For the PM task, participants were required to make a predefined response when two even numbers were presented together in the same trial. In a letter condition, pairs of letters were presented and participants had to decide which of the two letters (i.e., the left- or right-hand side of the computer screen) appeared first in the alphabet. For the PM task, participants were required to make a predefined response if two vowels were presented together in the same trial. Under these conditions (non-focal) successful PM performance is dependent on participants using information that goes beyond the processing requirements of the ongoing task (i.e., the ongoing tasks do not require participants to respond to two even numbers or two vowels). Accordingly, one would expect the aforementioned PM tasks to involve non-focal processing of the target cues. In line with this idea, there should be significant reliance on monitoring processes (see McDaniel & Einstein, 2000). PET analysis revealed changes in rCBF in areas of the anterior prefrontal cortex during prospective remembering. Increased PM demand was linked to decreased rCBF in the large left superior rostral medial frontal region of BA 10 as well as the middle temporal gyrus. Increased activation of the right dorsomedial thalamus was also observed with task conditions that required a PM component. The authors concluded that the medial and lateral rostral PFC are differentially involved in PM tasks such that the former is implicated in the suppression of intention generated thoughts and the latter in the maintenance of information.

A similar pattern of results was reported in a functional magnetic resonance imaging (fMRI) study which examined brain activation during different components of a PM task (Simons, Schölvinck, Gilbert, Frith, & Burgess 2006). Simons et al. (2006) manipulated the extent to which PM tasks depended on recognising the appropriate context to act (cue identification) and remembering the action to be performed (intention retrieval). While there were clear behavioural differences between cue identification and intention retrieval conditions, both PM components were associated with hemodynamic changes in the anterior prefrontal cortex (BA 10). Specifically, lateral BA 10 activation was accompanied by medial BA 10 deactivation especially when the demands on intention retrieval were high. A further fMRI study supported these findings by showing increased anterior prefrontal cortex activation during PM tasks which involved non-focal processing of a target (Reynolds et al., 2009).

Overall findings from the studies reported here (Burgess et al., 2003; Simons et al., 2006) highlight the involvement of anterior prefrontal cortex during non-focal (event-based) PM tasks. Burgess et al. (2003) explain that prefrontal activity may reflect processes associated with the maintenance of an intention including rehearsal in working memory (Gilbert Gollwitzer, Cohen, Oettingen & Burgess, 2009) and/or monitoring for a target (McDaniel & Einstein, 2011). If this assumption is correct, older adults might be expected to display impairment on non-focal PM tasks. This is because anterior prefrontal processes are suggested to decline with age (Jimura & Braver, 2010). Findings from behavioural studies are consistent with this proposal and demonstrate that older adults perform worse than younger adults on non-focal PM tasks (see Kliegel et al., 2008 for review).

Neuropsychology of focal (event-based) Prospective Memory tasks

Okuda et al. (1998) used PET to examine changes in rCBF in localised brain regions when participants were completing a focal PM task and a control task. Both tasks were accompanied by three isolated periods, i.e., a pre-PET scan period, a PET scan period and a post-PET scan period. Participants were aurally presented with Japanese nouns during the pre-PET scan period and the PET-scan period. During the pre-PET scan period, participants were presented with a list of 10 stimuli three times in a row. Participants were required to memorize the Japanese nouns as target stimuli and were also asked to try to retain them in memory for the duration of the PET scan period. During the PET scan period, participants were presented with 10 sets of five stimuli immediately followed by an inter-set blank duration. Participants were required to orally repeat the sequence of stimuli during the inter-set blank duration. In the post-PET scan period, participants were required to recall the 10 Japanese nouns which had previously been identified as target stimuli. The aforementioned procedures were identical for the focal PM task and the control task. However, in the focal PM task condition, participants were informed that the PET scan period would include some of the target stimuli. Since the target stimuli were encountered as a central aspect of the stimuli encoded during the PET scan period, this PM task is suggested to require focal processing of a target cue. Participants were instructed to tap with their left hand when they had orally repeated a target stimulus. No target stimuli were presented in the PET scan period of the control task. Participants completed both the focal PM task condition and the control task condition twice.

Surprisingly, several frontal regions were activated during focal PM task conditions relative to control task conditions. The right dorsolateral and vertrolateral prefrontal cortices, the left frontal pole and anterior cingulate gyrus, the left parahippocampal gyrus and midline medial frontal lobe all showed increased activation in the focal PM task conditions compared to control conditions. Increased activation in the right dorsolateral and ventrolateral prefrontal cortices was associated with holding and maintaining the intention of a future behaviour in memory. This result is consistent with a more recent finding which highlighted significant involvement of the dorsolateral prefrontal cortex in retaining the content for a future intention (Momennejad & Haynes, 2012). The dorsolateral prefrontal cortex has been linked to wider PM functions including responding to cues and retrieving a future intention from memory (Simons et al., 2006). In contrast, it is likely that the division of attention between two cognitive operations (repeating stimuli during the PET scan period whilst simultaneously checking for the presentation of target stimuli) caused increased activation in the medial frontal region. Furthermore, increased activation of the left parahippocampal region during the focal PM task may represent the process of novelty detection required for checking for target stimuli. The significant activation of several frontal regions in this study can be explained by the possible use of monitoring processes (Einstein et al., 2005) which are suggested to load on the frontal systems (Reynolds et al., 2009; Burgess, Scott & Frith, 2003).

In another study, Martin et al. (2007) used magnetoencephalogy (MEG) to examine neural activation during focal PM tasks. A total of five ongoing tasks were used and participants were required to respond to the presentation of focal targets. A number of the ongoing tasks required participants to identify which of two colours a circle appeared in, whilst one further task involved synchronous tapping to a flashing circle. In a focal PM task, participants were instructed to press a target key following the presentation of a target shape. The target shape was changed after each block of trials and in each case the target shape was presented on normal ongoing task trials. Thus, if a target shape was presented, participants were required to make a prospective response instead of an ongoing task response. Two further trials were included. Catch trials were distinguished by the presentation of non-target shapes (oddball) in which participants were instructed to ignore. RM trials involved the presentation of cue labelled “memory” where participants were required to press a particular key which was previously encoded with a target shape. MEG revealed different patterns of activation for PM conditions relative to oddball and RM conditions. With regard to the

posterior parietal region, onset latency was significantly faster after PM targets relative to oddball and RM targets. Furthermore, onset latency was faster in hippocampal regions on PM trials compared to oddball trials. Activation of the frontal region did not differ significantly across PM, oddball and RM trials. In conclusion, the research suggests that the posterior parietal region is implicated in noticing a focal target whilst the hippocampal region is involved in retrieving the intended action associated with a focal target

Assuming that focal PM tasks are generally less dependent than non-focal PM tasks on prefrontal regions and rely more on areas of the hippocampus, it might be expected that older adults to be relatively unimpaired on these tasks. This is because declines in prefrontal systems associated with aging (Jimura & Braver, 2010) should not lead to impairment on focal PM tasks. Findings which have shown no difference between older and younger adults on focal PM tasks support this view (Cherry & LeCompte, 1999; Reese & Cherry, 2002). More interestingly, a review of 18 studies reported an average 11% difference in focal processing between older and younger adults. This compared to an average 23% difference in non-focal PM tasks (McDaniel & Einstein, 2007). Thus, it might be that prefrontal regions have little involvement in focal PM tasks and as such age related declines in frontal processes have little effect on focal PM task performance.

Notwithstanding, the literature has been inconsistent. Some studies report increased activation in several frontal regions during focal PM task conditions (Okuda et al., 1998). Further classifications of focal PM task conditions including the length of the retention interval and/or perceived task importance may govern the extent to which these tasks rely on prefrontal systems.

3.2 Neuropsychology of time-based prospective memory

As noted previously, PM can be subdivided in terms of the retrieval cues available to people (i.e., event- and time-based PM tasks). We have already established that event-and time-based PM tasks differ in–terms of the quantitative involvement of rehearsal, self-initiated planning or spontaneous triggers (Kvavilashvili & Fisher, 2007). It is therefore possible that event- and time-based PM tasks place different demands on the neural system. To an extent, this proposal is supported in the literature and research has shown that patients who display abnormalities within the prefrontal cortex (e.g., cerebrovascular stroke; Brooks, Rose, Potter, Jayawardena & Morling, 2004 & Parkinson’s disease; Katai Maruyama, Hashimoto & Ikeda,

2003) demonstrate superior performance on time-based PM compared to event-based PM. Similar findings have been reported in patients with lesions to the prefrontal cortex. Cheng, Wang, Xi, Niu & Fu (2008) found significantly more event-based PM impairments in patients with lesions to the prefrontal cortex compared to healthy control participants (Cheng et al., 2008). However, findings from the same study failed to show any group differences in time-based PM performance.

In light of the apparent absence of time-based PM impairments in patients who have abnormalities in the prefrontal cortex, it is possible that time-based PM tasks implicate different aspects of the neural system. However, it is important to note that time-based PM tasks can be divided according to the duration of the delay between the formation of an intention and intention retrieval. As mentioned previously, short-term time-based PM tasks involve a relatively short delay interval between the formation of an intention and intention retrieval while long-term time-based PM tasks are governed by longer delay intervals. Thus, it might be that short- and long-term time-based PM place very different demands on the neural system.

Despite assertions that event-based PM may be more dependent on frontal regions compared to time-based PM tasks (Cheng et al., 2008; Katai et al., 2003), neuroimaging evidence has shown some evidence of frontal activation (as well as medial temporal activation) during the completion of time-based PM tasks with shorter delay intervals. Okuda et al. (2002) examined rCBF during an ongoing task, an ongoing task with an event-based PM cue and an ongoing task with a short-term time-based PM cue. While completing the ongoing task, participants were either asked to clasp their hands after a target cue had been presented (event-based PM) or after a specific time point (time-based PM). The total delay interval for the short-term time-based PM task was two-minutes where participants were required to clasp their hands once in the first 30 seconds, twice in the next 30 seconds, once in the third 30 seconds an once in the final 30 seconds. No clocks were available for participants to conduct regular time-checks and as such successful prospective remembering was entirely dependent on the self-estimation of time. Increased rCBF was observed in frontal and medial-temporal regions in both the event- and time-based conditions relative to the ongoing task only condition. However, initial analyses did not compare brain activation between event- and time-based PM tasks.

When Okuda et al‘s (2002) original data were analysed (Okuda et al., 2007) activation differences were found in the rostral prefrontal cortex during event- and short-term time-based PM tasks. Specifically, Okuda and colleagues’ (2007) reanalysis revealed significant rCBF increases in the left superior frontal gyrus (including in the lateral BA 10) in short-term time-based PM conditions relative to event-based PM conditions. Increased activation of the left superior frontal gyrus is suggested to represent the mental processes associated with the time estimation demands of time-based PM tasks. This assertion is supported by brain imaging data that has shown similar left superior frontal activation for tasks that require time estimation (Macar et al., 2002; Rao, Mayer & Harrington, 2001). Rao et al. (2001) found that activity in the left superior frontal area was heightened when participants engaged in time estimation as opposed to maintaining an intention with a requirement to act at a specific time.

Although left lateral BA 10 activation has also been associated with the maintenance of a delayed intention in event-based PM tasks (Burgess, Quayle & Frith, 2001), the region which was activated during the time-based PM tasks in the present study appear to be more superior to that area (Okuda et al., 2007). Furthermore, in the present study (Okuda et al., 2007), the location of the BA 10 which was activated during time-based PM tasks was not activated during event-based PM tasks. These findings suggest that there are multiple lateral BA 10 areas that are differentially involved in event- and time-based PM tasks. To be specific, Okuda et al. (2007) suggest that left BA 10 activation reflects a processing contribution to time-based PM tasks beyond that associated with the maintenance of intentions during event-based prospective memory tasks. On the other hand, event-based PM performance has been linked to deactivation of the medial BA 10.

Findings from a second study (Study 2) in Okuda and colleagues’ (2007) reanalysis identified regions of the rostral prefrontal cortex including the right superior frontal gyrus, the anterior medial frontal lobe and the anterior cingulate gyrus which were more active in short-term time-based PM conditions relative to event-based PM conditions. Characteristics of time-based PM tasks such as whether a clock is present and the subsequent removal of time estimation processes or not mediated the activation of the rostral prefrontal cortex.

To date, very few studies have explicitly explored the neural basis of long-term time-based PM tasks. One noteworthy investigation studied longer-term time based PM performance in patients with mesial temporal sclerosis (Adda et al., 2008). Mesial temporal sclerosis is a disorder which is characterised by selective neuronal loss in areas of the

hippocampus and thus any evidence of PM deficits is likely demonstrative of hippocampal degeneration. Adda et al. (2008) asked 48 patients with mesial temporal sclerosis (26 right lesions and 22 left lesions) and 26 control participants to complete an adapted version of the Cambridge Prospective Memory test (CAMPROMPT; Wilson et al., 2002). The CAMPROMPT is a laboratory task which consists of three event-based and three time-based PM tasks. However, in contrast to many studies which typically use PM tasks with short delay intervals (Einstein et al., 1995; Guynn et al., 1998; Smith, 2003), the current study adapted the CBPMT to include PM tasks with longer delay intervals. Level of time-based impairment was found to be significantly higher in patients who had left hippocampal lesions. There was a tendency for patients with left hippocampal lesions to perform worse than controls on event-based PM tasks although this difference fell just short of statistical significance. Adda and colleagues (2008) concluded that the hippocampus and in particular, the left hippocampal region is crucial to the performance of time-based PM tasks with long delay intervals.

In summary of the abovementioned findings, a number of rostral prefrontal regions appear to be implicated in short-term time-based PM performance. Specifically, the right superior frontal gyrus, anterior medial frontal lobe and anterior cingulate gyrus were associated with short-term time-based PM task performance (Okuda et al., 2002; 2007). By contrast, and on the basis of only one study that is available, the left hippocampal region appears to be involved in time-based PM tasks with long delay intervals (Adda et al., 2008). Clearly, further research is needed to explore the differing processing demands of short- and long-term time-based PM tasks.

3.3 Neurotransmitters and prospective memory

As noted previously, both the prefrontal cortex and the hippocampus are implicated in PM functioning. However interconnections between these regions may be fundamental for accurate PM performance. For example, the hippocampus sends direct excitory afferents to the prefrontal cortex to stimulate the activation on neurons and interneurons (Jay & Witter, 1991). The prefrontal cortex then sends indirect feedback projections to the hippocampus via the temporal cortex (Fuster, 1997). Damage to the prefrontal cortex has been linked to abnormal hippocampal neural activation associated with spatial localisation (Kyd & Bilkey, 2003). Thus, it appears that the prefrontal cortex plays a critical role in the activation of neurons in the hippocampus. It is suggested that mesocortical dopamine projections to the

prefrontal cortex are essential in the modulation of information processing by hippocampus-prefrontal cortex interactions (Bertolino et al., 2006; Seamans, Floresco & Phillips, 1998). For example, Bertolino et al. (2006) found that genetic deficits to a molecule involved in the clearance of dopamine in the prefrontal cortex (catechol-o-methyl transferase) affects hippocampus-prefrontal cortex interactions during memory processing.

In the context of PM, Goto and Grace (2008) found that retrospective information has to be incorporated into the prefrontal cortex to induce prospective information processing. This process is though to be mediated by the mesocortical dopamine system. Dopamine D1 receptor activation is involved in transporting hippocampal-based retrospective information to the prefrontal cortex. Once retrospective information is in the prefrontal cortex, dopamine D2 receptor activation is required for further processing of information to effect preparation of future intentions.

The serotonergic stystem also appears to be implicated in PM tasks. Meneses, Perez-Garcia, Ponce-Lopez, Tellez and Castillo (2001) suggest that serotonin (5-HT) has a modulatory role for neurocognition and, in particular that 5-HT uptake sites and HT $_{1\text{-}7}$ receptors are implicated in memory consolidation. Nonetheless, relatively little is understood about the neuropsychological function of 5-HT (Cowen & Lucki, 2011). Despite this, the serotonergic neurotoxicity that has been found in ecstasy users may in part explain the role of 5-HT in PM tasks. Increased lifetime ecstasy consumption has been linked to structural abnormalities within the serotonergic system including the degeneration of 5-HT axonal projections, abnormal regulation of 5-HT pathways and increased 5-HT$_{2A}$ receptor levels as a neuroadaptive response to reduced serotonin activity (Di lorio et al., 2012; Fischer Hatzidimitriou, Wlos, Katz & Ricaurte 1995). In an important study by Kish et al. (2010), reduced levels of 5-HT transporter binding were observed in all areas of the cerebral cortex and the hippocampus of ecstasy users. Importantly, serotonin transporter loss was reported at an average of 17% in the frontal cortex and 31% in the hippocampus in ecstasy users. Kish and colleagues (2010) concluded that chronic ecstasy use might induce degeneration of serotonergic neurons within the cerebral cortex and the hippocampus. In addition, the authors note the possibility that 5-HT changes may mediate behavioural problems observed in some ecstasy users. These findings have important implications for PM performance and may go some way to explaining the modulatory effect of 5-HT in performance. For instance, it is understood that the hippocampus is involved in event-based PM tasks that require

spontaneous retrieval processes (Moscovitch, 1998), in checking for target stimuli (Okuda et al., 1998) and in the retrieval of delayed intentions associated with target stimuli (Martins et al., 2007). Furthermore, Adda et al. (2008) found that the hippocampus plays an important role in time-based PM tasks where there is a long delay between the formation of an intention and its subsequent retrieval from memory (i.e., in long-term time-based PM tasks). Thus, degeneration of the %-HT system within the hippocampus may clearly impair event- and time-based PM performance. The PFC is also implicated in PM tasks and is associated with the maintenance of an intention (Gilbert et al., 2009) and the monitoring for PM targets (McDaniel & Einstein, 2011) in event-based PM tasks. The PFC is also involved in time-based PM tasks and, in particular during the encoding of information relating to "what" an intention is and "when" it should be carried out (Momennejad & Haynes, 2012). To summarize, the lower serotonin transporter densities that have found in PM-related brain regions in ecstasy users (the hippocampus and the PFC; Kish et al., 2010) could have negative implications for both event- and time-based PM performance.

3.4 Chapter Summary

The current Chapter has identified several regions of the neural system that appear to be implicated during event- and time-based PM tasks. Event-based PM tasks that require non-focal processing of target events have been linked to the anterior prefrontal cortex (Burgess et al., 2003; Reynolds et al., 2009) and more specifically to lateral BA 10 activations and medial BA 10 deactivations. Neurological changes within the prefrontal regions might reflect the processes associated with the maintenance of an intention (Burgess et al., 2003; Momennejad & Haynes, 2012), retrieving the future intention from memory (Simons et al., 2006) and/or the monitoring processes associated with a directed search for a target event (McDaniel & Einstein, 2000). Event-based PM tasks that require focal processing of target events appear to load on medial temporal regions including the hippocampus. Activation changes within the hippocampus have been linked to the retrieval of an intention associated with a focal target (Okuda et al., 1998).

Several areas of the rostral prefrontal cortex also appear to be implicated in time-based PM tasks. Activation of the left superior frontal region is suggested to reflect the processes associated with time estimation whereas activation of more diverse regions of the

rostral prefrontal cortex (e.g., right superior frontal gyrus, anterior medial frontal lobe, anterior cingulated gyrus) has been found in time-based PM tasks where time estimation is not needed (i.e., where clocks are provided) (Okuda et al., 2007). Overall, the literature suggests that event- and time-based PM tasks place different demands on the rostral prefrontal cortex with some event- (i.e., focal PM tasks) and time-based tasks (i.e., those with longer delay periods, Adda et al., 2008) also loading on medial temporal regions.

Aside from frontal and medial temporal regions, the parietal cortex has also been linked to PM functioning. For example, the BA7 is suggested to have important implications in event- and time-based PM tasks in storing future intentions in memory (Benoit, Gilbert, Frith & Burgess, 2012) while lateral and more superior regions have been linked to responding to cues and retrieval of future intentions from memory (Simons et al., 2006)

In discussing drug-related neurotoxicity, Chapter 4 explains how cannabis, ecstasy, cocaine and other drugs may affect brain regions associated with PM performance. In consideration of the present thesis which aims to explore PM deficits in ecstasy users, specific emphasis is placed on how the neural effects of ecstasy use might be linked to PM impairments.

Chapter 4: The neurotoxic potential of drug use

Chapter outline

In consideration of the evidence put forward in Chapter 3 which provides a thorough account of the brain regions and neural networks implicated in PM tasks, the present Chapter discusses the neurotoxic potential of licit and illicit drugs. The literature is used to determine whether impairments to specific brain regions and/or neurotransmitters may mediate apparent PM deficits in drug users. Particular attention is given to the neurotoxic potential of ecstasy use and to whether potential neural abnormalities may impair performance on PM tasks.

4.1 Neurotoxic potential of cannabis

The acute effects of cannabis use include loss of internal control and cognitive impairment in attention and memory (Hall, Johnston & Donnelly, 1999). However, the psychological effects and health implications of chronic cannabis use are unclear. On the whole, it seems that cannabis use can induce cognitive impairments which persist beyond acute intoxication. A recent investigation that used an extensive battery of event- and time-based measures of PM found clear evidence of PM deficits in currently abstinent cannabis users (Hadjiefthyvoulou et al., 2011a). Other studies have however failed to demonstrate conclusive evidence for cannabis-related impairments in PM (McHale & Hunt, 2008). McHale and Hunt (2008) found no differences between chronic cannabis users and non-users in terms of event-based PM on the Rivermead Behavioural Memory Test (*Message* Subset). However, chronic cannabis users did differ significantly from non-users on both short- and long-term, time-based measures of PM**.** The inconsistency between the findings warrants the possibility that some cannabis-related PM impairments may be reversible after a prolonged period of abstinence from the drug (Lundqvist, 2005). Alternatively, cannabis use may only affect the neural mechanisms associated with specific types of PM tasks whilst leaving other regions relatively unaffected. In order to investigate this proposal and to identify specific brain regions and neuromodulatory mechanisms that might underpin PM impairment, it is important to consider the neurotoxic potential of cannabis use.

Cannabis is a plant that is made up of several chemical agents known as cannabinoids. ^{9}tetrahydrocannabinol (THC) is one particular cannabinoid that has been linked to the psychoactive properties of cannabis (Gaoni & Mechoulam, 1964). THC is a highly lipophilic

component that exerts its effects by binding to CB1 cannabinoid receptors (Ameri, 1999). The majority of CB1 binding sites are distributed within several regions of the brain including the basal ganglia, the molecular layer of the cerebellum, the dentate gyrus and some layers of the cortex (Ameri, 1999). Furthermore, high densities of CB1 receptors are located in brain regions implicated in PM functioning, including within the prefrontal cortex (PFC) and the hippocampal regions (Herkenham et al., 1990). A range of functional and structural neuroimaging techniques have been used to investigate changes within the brain resulting from cannabis use. Data relating to the effects of cannabis use on PM-related brain regions is discussed below.

The use of cannabis has been associated with significant functional abnormalities in areas of the frontal cortex. Matthew and Wilson (1991) used single-photon emission computed tomography (SPECT) and found that acute administration of cannabis in humans was associated with increased cerebral blood velocity and bilateral increases in cerebral blood flow in the frontal region. Importantly, abnormalities in the frontal region appear to remain for several weeks after last exposure to the drug. However, it is important to clarify that increased activity in the PFC appears to follow acute cannabis intoxication while diminished activity in this region has been linked to chronic exposure to the drug. For example, chronic exposure to cannabis in rats results in decreased mesolimbic dopaminergic activity and diminished activation in the PFC (Diana, Melis, Muntoni & Gessa, 1998; Verrico, Jentsch & Roth, 2003). Similar findings are reported in humans. Lundqvist, Jönsson and Warkentin (2001) found reduced blood flow in the right frontal region of cannabis dependent persons. In another study, Eldreth, Matochik, Cadet and Bolla (2004) employed positron emission tomography and used a modified version of the Stroop task to examine brain activation and executive functions in 25-day abstinent cannabis users. Cannabis users displayed no deficits in executive functions relative to nonusers. However, hypoactivity in the left lateral PFC was observed in cannabis users suggesting that cannabis use has persistent effects on brain activity.

Data from animal studies have highlighted significant morphological changes in the hippocampus after administration of THC (Rubino et al, 2008; Tagliaferro et al, 2006). Rubino et al. (2008) administered THC via an ethanol, cremophor and saline solution to a sample of rats (35 to 45 post natal days). The rats were then left undisturbed until adulthood (75 post natal days) where aversive and spatial working memory was assessed. THC treated rats performed worse than rats were not treated with THC on the spatial working memory

task. After reviewing levels of marker proteins within the hippocampus, Rubino and colleagues (2008) concluded that the administration of THC dampens synaptic contacts and/or synaptic connections throughout the hippocampus and this effect may underpin cognitive deficits that follow THC treatments.

In consideration of the functional neuroimaging evidence, data from EEG studies suggests that THC reduces the activation of a number of frequency bands in the hippocampus and neocortex in humans, rabbit and rodents (Ilan, Smith & Gevins, 2004; Buonamici, Young & Khazan, 1982; Robbe et al., 2006; Willinsky, Loizzo & Longo, 1975). In one study, Robbe et al. (2006) examined local field potential recordings in rats and found evidence that both THC and the CB1 agonist, CP, 55940 decrease the power of theta (4-10 Hz), gamma (30-8-Hz) and fast ripple (100-200 Hz) oscillations in the hippocampus. This is significant in terms of PM functioning and the formation of new memories because hippocampal theta and gamma oscillations are involved in the coordination of synchronous firing between the hippocampus and the cortex (Siapas, Lubenov & Wilson, 2005). The abnormalities found in the fast ripple oscillations are also important in that they appear to facilitate the transfer of hippocampal memory traces to neocortical circuits for long-term memory storage (Karlsson & Frank, 2009). This is particularly important in the context of long-term PM tasks where there are long delay periods between the formation of an intention and its subsequent retrieval from memory. Abnormal functioning of fast ripple oscillations may therefore lead to problems in the transfer of delayed intentions to long-term memory.

Using PET, Mathew et al. (2002) found increased cerebral blood flow in the hippocampus after THC infusion. However, increased cerebral blood flow in the hippocampus was specific to the acute effects of THC infusion. Hippocampal-related changes in cerebral blood flow returned to baseline levels 60-minutes after THC infusion. Similar findings were reported by Block et al. (2002) who used PET to compare memory-related regional cerebral blood flow between cannabis users (average abstinence period of 28 hours) and nonusers. Relative to nonusers, cannabis users displayed increased blood flow in memory-relevant regions of the cerebellum, altered lateralisation in the hippocampus as well as decreased blood flow in the PFC. Importantly, these changes were accompanied by verbal learning deficits in cannabis users. Nonetheless, given that participants in this study were only abstinent for a period of 26 hours, post intoxication effects may have confounded the results. This view is consistent with findings from another task-based study which showed

that verbal learning was impaired in cannabis users at seven days post drug use but returned to baseline after 28 days (Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001).

Some studies have also associated cannabis use with decreased activation in the hippocampus. Functional magnetic resonance imaging data has shown that that cannabis users (who had abstained from cannabis use for 7 days prior to testing) display decreased activation in the hippocampus and the right dorsolateral PFC compared to nonusers during the completion of an associative learning task (Jager et al., 2007). However, this abnormality was not accompanied by a deficit in associative learning. Thus, it appears that decreased brain activation in the hippocampus does not always predict cognitive performance. By way of explanation, it is possible that frequent cannabis users were experiencing withdrawal effects after abstaining for the seven day period. For example, withdrawal effects may have dampened activity within memory-related regions of the brain without directly affecting cognitive performance (Jager et al., 2007).

The different activation levels of PM-related brain regions which have been observed in the literature may reflect differences between the abstinence periods and overall lifetime exposure to cannabis across studies. For example, cannabis users in Jager et al's (2007) study abstained from cannabis use for a period of seven days prior to testing. This compares to considerably shorter abstinence periods in studies which have found cannabis related increases in the activation of memory-related brain regions (Block, Erwin & Ghoneim, 2002; Kanayama, Rogowska, Pope, Gruben & Yurgelun-Todd, 2004). Thus, studies with lower abstinence periods may reflect the post acute effects of cannabis use while studies with longer abstinence periods (Jager et al., 2007) might demonstrate the more sustained effects of the drug.

In humans, the evidence is mixed as to whether cannabis induces structural changes in the hippocampus. Jager et al. (2007) used voxel-based morphometry and found no differences in hippocampal brain tissue composition between cannabis users and nonusers. This finding is consistent with several studies which report no evidence of hippocampal structural changes in adolescent cannabis users (Block et al., 2000; Tzilos et al., 2005). Alternatively, some studies have shown clear structural abnormalities in the hippocampus of cannabis users. Matochik, Eldreth, Cadet & Bolla (2005) found that chronic cannabis use was associated with abnormalities in gray matter tissue composition in the parahippocampal gyrus and with increased white matter density in the parahippocampal gyri. Two more recent

studies have also found reduced hippocampal volumes in heavy cannabis users (Cousijn et al., 2012; Schacht, Hutchinson & Filbey, 2012). Cousijn et al. (2012) found that increased use of cannabis was associated with lower grey matter volumes in the hippocampus in heavy cannabis users. Further research from Yucel et al. (2008) noted a 12% reduction in hippocampal volumes of long-term heavy cannabis users relative to non-cannabis users. More recent evidence lends support to these findings and has also observed significantly reduced hippocampal volumes in heavy cannabis users relative to healthy controls (Schacht et al., 2012).

To conclude, there is strong evidence for the neurotoxic potential of cannabis use in animals and in humans. Cannabis' effects on PM-related brain regions such as the PFC and the hippocampus have been well documented. Heavy cannabis use has been associated with structural changes in the hippocampus but not in the PFC. Despite this, there appears to be increased activity within the PFC and the hippocampus during immediate exposure to cannabis and a dampened response during abstinence.

4.2 Neurotoxic potential of ecstasy/MDMA

Ecstasy is a recreational drug (Curran et al., 2004) which acts primarily by stimulating the release of monoamines such as serotonin (5-HT) and dopamine (DA) (Green, Cross & Goodwin, 1995; Ricaurte & McCann, 2001). Long-term exposure to ecstasy may also induce decrements in markers of monoamine neurons (Ricaurte et al., 1988). It does this through its principle ingredient, ^{3,4}Methylenedioxymethamphetamine which in currently abstinent users has been associated with reduced levels of brain 5-HT, its primary metabolite 5-hydroxy-indoleacetic acid (5-HIAA), the 5-HT transporter (SERT) and tryptophan hydroxylase (Ricaurte DeLanney, Wiener, Irwin & Langston, 1988a; Ricaurte, Martello, Katz & Martello 1992). Moreover, abnormalities in monoamine neurons appear to persist for years after last exposure to ecstasy suggesting that any observed effects may be long-lasting (Taffe et al., 2003; Reneman et al., 2002).

In humans, exposure to ecstasy is followed by the acute release of 5-HT from pre-synaptic 5-HT neurons (Nishisawa, Mzengeza & Diksic, 1999). This is often associated with short-term "positive" feelings of elevated mood (Liechti & Vollenweider, 2001), extroversion and increased sensory perception (Farré et al., 2007). However, repeated exposure to ecstasy

can induce long-term damage to 5-HT neurons in PM-related brain regions. Pharmacological challenges have been used to identify abnormalities in the regulation of endocrine secretion because of imbalances in the 5-HT system (Gouzoulis-Mayfrank & Daumann, 2006). Specifically, pharmacological challenge studies aim to increase the rate of production of 5-HT via the administration of 5-HT agonists such as fenfluramine or L-Tryptophan. The subsequent secretion of cortisol, prolactin and other hormones, and in particular their concentrations in the peripheral blood are then measured to investigate any irregularities in their homeostatic regulation.

Gerra et al. (2000) found that compared to control participants, ecstasy users (abstinent for 3-months) displayed reduced prolactin and cortisol responses to fenfluramine. Similarly, Price, Ricaurte, Krystal & Heninger (1989) found impairments in prolactin responses to L-Tryptophan in participants with a history of heavy ecstasy use. Due to the involvement of 5-HT in the secretion of prolactin and cortisol, it appears that ecstasy use might induce long-term 5-HT neurotoxicity. Nonetheless, it is worth noting that in Gerra et al's (2000) study, prolactin and cortisol responses in ecstasy users were equivalent to those of nonusers following a 12-month period of abstinence from the drug. This suggests that apparent long-term damage to 5-HT integrity may be reversed after a sustained period of abstinence from the drug.

Neuroimaging techniques have also been used to examine 5-HT functioning in ecstasy users. These studies commonly compare individual levels of SERT binding to examine brain 5-HT integrity in ecstasy users and nonusers. SERT is the site on 5-HT neurons which is responsible for taking 5-HT back into the neuron. Decreased brain SERT levels are found in animals exposed to serotonergic neurotoxins and as such SERT binding is suggested to reflect 5-HT neuron integrity (Brown & Molliver, 2000). Radioligand-based methods are commonly used to measure SERT binding in ecstasy users. Using PET, McCann Szabo, Scheffel, Dannals & Ricaurte (1998) reported reduced densities of 5-HT transporter sites in ecstasy users compared to nonusers. Crucially, these abnormalities were apparent in PM-related and non PM-related brain regions including the frontal cortex, the hypothalamus, the cingulate cortex and the occiptal and parietal cortex.

In another neuroimaging investigation of SERT binding, Semple et al. (1999) used the radioligand, [123I]b-CIT in a SPECT procedure in 10 ecstasy users and 10 nonuser controls.

In contrast to McCann et al's (1998) findings, Semple and colleagues (1999) found normal SERT binding levels in the striatum, midbrain, and thalamus in ecstasy users. Ecstasy users displayed slight reductions in SERT binding in non PM-related areas of the cerebral cortex (occiptical, cingulate, and calcarine). Despite this finding, the use of the [123I]b-CIT as a measure of SERT is questionable. This is because [123I]b-CIT is not specific to SERT binding and is sensitive to both dopamine and noradrenaline transporters (Kish, 2002). Moreover, Heinz and Jones (2000) criticise that the use of [123I]b-CIT for measurements of SERT binding in areas of very low SERT density. The cerebral cortex is one area of the human brain which is packed with several transporters and where SERT density is relatively low (Heinz & Jones, 2000). As a result, it is difficult to determine whether diminished cortical [123I]b-CIT binding reported in Semple et al's (1999) investigation is demonstrative of decreased levels of SERT or other transporters.

In addressing the issues outlined above, Kish et al. (2010) employed SERT binding as a primary outcome measure and used a PET radioligand ([11C]DASB) which has the specific ability to assess regional binding in the cerebral cortex and subcortical areas. Magnetic resonance imaging (MRI) for PET image co-registration and structural analyses were conducted on a relatively large sample of 49 chronic ecstasy users (mean abstinence period of 45 days) and 50 nonuser controls. Reduced levels of 5-HT transporter binding were observed in all areas of the cerebral cortex and the hippocampus of ecstasy users. In terms of PM-related brain regions, SERT loss was reported at an average of 17% in the frontal cortex and 31% in the hippocampus in ecstasy users. Interestingly, ecstasy users displayed normal levels of 5-HT transporter binding in the striatum despite this region being heavily packed with serotonergic neurons. Kish et al. (2010) concluded that serotonergic neurons within the cerebral cortex and the hippocampus are particularly susceptible to the effects of chronic ecstasy use and that behavioural problems observed in some ecstasy users may be mediated by 5-HT transporter changes within the cerebral cortex. Cortical thinning was evident especially in left hemisphere locations including the superior (BA6) middle (BA10 and BA9) and inferior (BA47) frontal gyri, inferior parietal (BA40), middle temporal gyrus (BA22), occipital cortex (BA17) and right inferior parietal. Furthermore the neural deficits evident in ecstasy/polydrug users were associated with aspects of prior ecstasy consumption (Kish et al., 2010).

Neuronal damage in ecstasy users has been further investigated through post-mortem brain examination. One advantage of post-mortem investigations over and above neuroimaging studies is that they allow for detailed examination of all markers of 5-HT nerve terminal integrity. In a post-mortem investigation of a chronic ecstasy user, who also used cocaine and opiate drugs, Kish (2000) found low levels (between 60% and 77% reductions) of 5-HT but normal dopamine concentration in the striatum. Findings which have shown no reduction of 5-HT in cocaine (Wilson et al., 1996) and heroin (Kish et al., 2001) users would suggest that the observed effects are attributable to the long-term use of ecstasy.

Aside from MDMA-induced 5-HT neurotoxicity, MDMA exposure can also result in abnormalities within the DA system (Crespi, Mennini & Gobbi, 1997; Koch & Galloway, 1997; Mann, Ladenheim, Hirata, Moran & Cadet, 1997). Shortly after MDMA administration, acute increases in DA can be found across several brain regions including the nucleus accumbens (Cadoni et al., 2005) the PFC (Nair & Gudelski, 2004) and the hippocampus (Shankaran & Gudelski, 1998). Gerra et al. (2002) used a pharmacological challenge test to investigate the long-term effects of MDMA exposure on DA. The DA agonist, Bromocriptine (BROM) was administered to a sample of ecstasy users (abstinent for three weeks) and drug naive controls to investigate its effects on prolactin (PRL) and growth hormone (GH) levels. Findings showed that BROM suppression elicited no differences between the PRL responses of ecstasy users and nonusers. However, significantly lower GH levels were observed in ecstasy users compared to non-users following BROM stimulation. Conclusions from this study suggest that the reduced GH levels in ecstasy users may reflect an abnormal sensitivity of D2 receptors in the hypothalamus as a consequence of continued MDMA exposure. This finding is particularly interesting in light of animal data showing a direct link between DA receptors and PM performance. Specifically, D1 receptors are suggested to support functions of RM tasks while D2 receptors support functions of PM tasks (Goto & Grace, 2008). Abnormal DA functioning in ecstasy users was also found by Sekine et al. (2003). The authors used PET analysis and found that relative to non-users, ecstasy users exhibited lower levels of DA transporters in several brain regions including the PFC (Sekine et al., 2003). This finding is significant considering that successful PM performance is dependent on prefrontal executive processes.

More recent investigations have suggested an important role of cortisol in MDMA neurotoxicity. For example, in laboratory studies, administration of MDMA stimulates the

hypothalamus-pituitary adrenal (HPA) axis resulting in increased plasma concentrations of cortisol (Parrott, 2009). In a study which examined salivary cortisol in ecstasy users, Parrott, Lock, Conner, Kissling & Thome (2008) found increases of up to 800% in participants who were clubbing and on drug compared with baseline and compared with dancing when drug free. In a similar study, Wolff et al. (2012) evaluated cortisol levels pre and post clubbing. At baseline, cortisol levels were elevated in clubbers compared with normal population and diurnal norms. The post clubbing data revealed that clubbers who had consumed ecstasy tablets also had elevated cortisol levels compared with those individuals who had not consumed ecstasy. Genetic based differences in drug metabolism mediated these effects. More specifically, post-clubbing increases in cortisol were largely limited to two CYP2D6 phenotypes characterised by poor or intermediate metabolism. Furthermore, those participants with the COMT genotype (met/met) which is associated with low activity drug metabolism, registered large increases in cortisol post clubbing regardless of whether they had taken ecstasy or not. Overall, it appears that the regular use of ecstasy may give rise to HPA axis dysregulation. In light of this evidence, it is possible that MDMA induced, cortisol mediated, HPA dysregulation may be responsible for some of the cognitive deficits observed in ecstasy users. For example, cortisol is highlight implicated in learning and memory as well as attentional processes. This effect is characterised by an inverted-U shaped curve where too much or too little cortisol can lead to cognitive impairment. Crucially, cortisol is implicated during the regulation of DA which is important for PM functioning (Goto & Grace, 2008). Moreover, chronically elevated levels of cortisol have been linked to PM-related brain regions including the PFC and the hippocampus (Erickson, Drevets & Schulkin, 2003). Overall, it seems that the use of MDMA may increase cortisol and thus, disrupt dopamine regulation in PM-related brain regions.

In summary, there is evidence for serotonergic and to a lesser extent dopaminergic neurotoxicity in ecstasy users. Ecstasy use has been shown to induce serotonergic damage in PM-related brain regions including in the frontal cortex (McCann et al., 1998; Kish et al., 2010) and in the hippocampus (Kish et al., 2010). Impairments of 5-HT functioning in these regions may underpin PM deficits in ecstasy users. Ecstasy users also display lower levels of DA transporters in the PFC. Importantly, abnormalities that have been found in the functioning of DA D2 receptors in ecstasy users (Gerra et al., 2002) are those that are thought to be an integral component of successful PM functioning (Goto & Grace, 2008).

Aside from evidencing ecstasy-related deficits in the serotonergic and dopaminergic systems, the literature has identified clear structural changes in PM-related brain regions in ecstasy users. Daumann et al. (2011) examined the extent to which increased exposure to MDMA can affect the structure of different brain regions. Daumann and colleagues (2011) studied gray and white matter densities in 20 frequent ecstasy users, 42 less frequent users and 16 drug-naive controls. Using fMRI and voxel-based morphometry, Daumann and colleagues (2011) compared grey matter volume in a number of brain regions between the groups. Compared to the low frequency group, frequent ecstasy users demonstrated lower grey matter volume in medial frontal regions including in the orbital and medial frontal cortex. These results support previous findings which have shown that ecstasy users display decreased grey matter in a number of brain regions localised to the neocortex in bilateral occiptical cortex (BA10), the left middle temporal gyrus (BA21) and the left inferior frontal gyrus (BA45). The implications of the findings suggest that repeated exposure to ecstasy may increase structural changes in medial frontal regions. Given the role of frontal regions in prospective remembering, structural changes in the medial frontal region may compromise ecstasy users' functioning on PM tasks.

Further structural changes have been observed in other PM-related brain regions. A recent study by Hollander et al. (2012) examined hippocampal volume in chronic ecstasy users and polydrug user controls. Significantly smaller hippocampal volumes were found in ecstasy users relative to polydrug user controls. To be specific, hippocampal volumes were, on average, 10.5 % smaller in ecstasy users compared to polydrug user controls. The only significant difference between the two user groups was the extent of prior ecstasy use. Participants in the ecstasy user group had each consumed a minimum of 50 ecstasy tablets whereas participants in the polydrug user control group reported no ecstasy use. Crucially, participants in the ecstasy user group were on average drug free for more than two months suggesting that ecstasy use can induce a long-lasting decrease in hippocampal volume.

4.3 Neurotoxic potential of cocaine

The following paragraphs discuss the effects of cocaine on brain function and structure in an attempt to identify the underlying mechanisms that underpin psychological impairments. Animal-based studies point towards diminished DA integrity in the rodent brain following exposure to cocaine. With regard to PM-related brain regions, Wyatt, Karoum, Suddath &

Fawcett (1988) found decreased levels of DA in the frontal cortex of rats that were injected with a cocaine solution twice daily for a period of seven days. Although this finding could potentially have important implications for PM functioning, the drug regimen used in this study does not reflect typical cocaine consumption patterns in humans. That is, cocaine users may have a tendency to binge over a number of days and then remain abstinent for an extended period of time (see Zeigler, Lipton, Toga & Ellison, 1991). In an attempt to investigate the patterns of binging which are commonly seen in human cocaine users, Zeigler et al. (1991) employed a silastic pellet technique which released cocaine at a steady rate over a number of days. Rats were either administered with continuous cocaine (silastic pellet), cocaine injections, continuous amphetamine (silastic pellet) or a control solution containing no drug over a five-day period. This was followed by a drug free period of 30 days. In vitro autoradiography showed large increases in D2 binding and large decreases in D1 binding in DA rich regions after continuous amphetamine administration. Conversely, continuous cocaine administration was followed by increased benzodiazepine binding in the cortex and the amygdala and decreased muscarinic acetylcholine receptor binding in the hippocampus. These alterations in brain chemistry show that amphetamine and cocaine can induce long-lasting effects on neurochemical systems and neural regions associated with PM functioning (e.g., D2 receptors and the hippocampus).

Tomasi et al. (2007) investigated the possibility that cognitive dysfunction in cocaine users might be linked to impairments of cortical and subcortical regions modulated by dopamine. The authors used fMRI to study brain activation during a verbal working memory task in cocaine abusers and healthy controls. Cocaine abusers displayed hypoactivation in the mesencephalon compared to controls. This is interesting given that this region is densely populated with dopamine neurons. Relative to controls, cocaine users also showed larger deactivation in dopamine projection regions (putamen, anterior cingulate, parahippocampal gyrus, and amygdala) and hyperactivation in cortical regions involved with attention (prefrontal and parietal cortices) and PM (PFC). In the working memory task, activation was lower in the prefrontal and parietal cortices in cocaine abusers when compared with controls. This finding may demonstrate limited network capacity in cocaine users compared to nonusers. This is particularly potent in the context of PM and in light of evidence that suggests that PM is mediated by executive functioning processes (Heffernan & Bellis, 2012; Kopp & Thöne-Otto, 2003; Martin et al., 2003). Overall, these findings provide evidence of impaired function of brain regions involved with executive control, attention and PM in

cocaine abusers. These neurofunctional abnormalities together with abnormal dopamine functioning might underpin cognitive deficits during early cocaine abstinence.

Structural neuroimaging evidence has shown lower densities of gray matter in the PFC of cocaine users compared to nonusers (Matochik et al., 2003). Lower levels of gray matter were found in the cingulate gyrus, lateral PFC, and medial and lateral parts of the orbitofrontal cortex. These findings are in line with other structural neuroimaging studies which have shown reduced gray matter volumes in the frontal cortex of cocaine users (Franklin et al., 2002; Sim et al., 2007). Thus, it appears that the frontal cortex is particularly susceptible to cocaine-related volume changes and that abnormalities in the prefrontal region may contribute to any PM dysfunction observed in cocaine users. These findings are further supported by functional neuroimaging work which has shown clear dysfunction of the PFC of cocaine users (Bolla et al., 2004; Volkow, Mullani, Gould, Adler & Krajewski, 1988; Volkow et al., 1992). Using PET, Volkow et al. (1988) found decreased rCBF in chronic cocaine users compared to nonusers. Additionally, lower levels of metabolic activity have been found in the PFC of cocaine users compared to nonusers (Volkow et al., 1992). Importantly, deficits within the PFC persist after a period of abstinence from cocaine use (10 days, Volkow et al., 1998; 3 weeks, Volkow et al., 1992).

Similarly, Bolla et al. (2004) employed PET and found that compared to nonuser controls, cocaine users displayed abnormal functional activation in the PFC whilst completing an executive functioning task. This finding is of particular interest in the context of PM performance since PM has been shown to recruit executive resources (Martin et al., 2003). Compared to nonusers, cocaine users displayed lower levels of activation in PM-related brain regions including in the anterior cingulate cortex (Okuda et al., 1998; 2007) and the lateral PFC (Okuda et al., 2007). Specifically, average dose of cocaine (per week) was negatively correlated with activity in the rostral anterior cingulate cortex and the lateral PFC.

4.4 Neurotoxic potential of tobacco and alcohol

A number of studies have associated chronic cigarette smoking with global brain impairments (Akiyama et al., 1997; Hayee, Haque, Anwarullah & Rabbani, 2003). Moreover, chronic smoking has been linked to abnormalities in PM-related brain regions including the

PFC (Sutherland, Ross, Shakleya, Huestis & Stein, 2010; Zhang, Stein & Hong, 2011), anterior frontal lobe (Brody et al., 2004), cingulate gyrus (Gallinat et al., 2006) and the hippocampus (Gallinat et al., 2007; Li, Park, Bahk & Kim, 2002). Zhang et al. (2011) explored white matter integrity and gray matter density in 48 smokers and 48 non-smokers. Voxel-based morphometry revealed that smokers displayed lower gray matter density in the PFC. Prefrontal cortical gray matter density was negatively correlated with total lifetime tobacco use. In addition, fractional anisotropy showed that smokers who were heavily dependent on tobacco displayed significant lower fibre integrity in the left PFC. These findings are consistent with other studies which have reported prefrontal cortical damage in cigarette smokers (Brody et al., 2004; Gallinat et al., 2006). Sutherland et al. (2010) used fMRI and found that relative to non-smokers, smokers displayed greater tonic activation in the medial superior frontal cortex, right anterior insula and the bilateral anterior PFC during working memory task completion. These findings show that smokers require additional recruitment of working memory and supervisory control operation to perform working memory tasks. Sutherland and colleagues' findings may have important implications for PM task performance given that both the PFC and working memory (Heffernan & Bellis, 2012) have been linked to PM. Thus, it is plausible that smokers may need to recruit additional PM operations including enhanced PFC activation to carry out PM tasks. Further smoking-related damage to the PFC was found by Gallinat et al. (2006). Gallinat and co-workers used MRI and found that smokers displayed lower gray mater volumes in frontal, temporal and occipital regions relative to non-smokers. Similar findings were reported by Brody et al. (2004). MRI data showed that smokers displayed lower volumes and densities in PFC and anterior frontal lobe gray matter. Smokers also showed smaller volume of the left dorsal anterior cingulate gyrus, and lower gray matter density of the right cerebellum relative to non-smokers.

Damage to other PM–related brain regions has also been found in cigarette smokers. For example, lower N-acetylaspartate levels have also been found in the left hippocampus of smokers compared to non-smokers (Gallinat et al., 2007). Furthermore, human post-mortem studies of lifelong smokers have shown evidence of increased binding of nicotine in the hippocampus (Breese et al., 1997). A significant positive correlation was found between exposure to tobacco and the number of nicotine receptor binding sites in the hippocampus. Although a dose-dependent increase in hippocampal-nicotinic receptor binding was observed, these changes were shown to be reversible after a prolonged period of abstinence from cigarette smoking.

The use of other licit drugs can have detrimental affects on the brain. For example, there is substantial evidence that chronic alcohol consumption has profound effects on the structure and function of the PFC and the hippocampus. This evidence stems from human and animal studies, behavioural, brain imaging and molecular and cellular observations. For example, the chronic use of alcohol has been associated with changes in the structural morphology and integrity of the PFC. Early research has shown that alcohol dependent subjects display lower levels of gray matter in the PFC (Jernigan et al., 1991) and reduced white matter in the cortex (de la Monte, 1998). Furthermore, long-term chronic alcohol exposure has been associated with volume loss within the frontal lobes (Pfefferbaum, Sullivan, Mathalon & Lim, 1997). More recent findings have linked the chronic use of alcohol to reduced integrity of prefrontal white matter (Pfefferbaum & Sullivan, 2005; Harris et al., 2008).

Chronic alcohol users also display functional abnormalities in the PFC (Pfefferbaum et al., 2001). They found that alcohol users display differential patterns of activation in the PFC during the completion of executive functioning tasks. This finding suggests that there are alterations to the way in which the brain performs these tasks. Similarly, Crego et al. (2010) found that compared to control subjects, binge drinkers had hyperactivation of the right PFC. Furthermore, research indicates that poor performance on executive function tasks might be linked to alcohol-related prefrontal impairments. Adams et al. (1993) found that performance on an executive functioning task was associated with decreased medial frontal glucose metabolism. Similarly, Oscar-Berman and Marinkovíc (2007) found that alcohol-related deficits in executive functions that involve monitoring processes were related to abnormal prefrontal activation. The evidence outlined above shows a clear relationship between the chronic use of alcohol and PFC impairment. Importantly prefrontal abnormalities which result from alcohol abuse have been associated with executive functioning deficits. This finding is noteworthy in the context of this thesis given the potential role of executive processes in PM performance (Heffernan & Bellis, 2012).

Abnormalities in more diverse brain regions in additional to those found in PFC have been observed following chronic alcohol exposure. For example, chronic alcohol administration has been associated with significant proteomic changes in the hippocampus of rats (Hargreaves, Quinn, Kashem, Matsumoto & McGregor, 2009), as well as reduced hippocampal serotonin transporter density in monkeys (Burnett, Davenport, Grant & Friedman, 2012). Further animal research with rats has associated chronic alcohol exposure

with hippocampal neurogenesis (He, Nixon, Shetty & Crews, 2005). Hippocampal neurogenesis may have negative consequences for cognitive performance given that it is associated with lower cell survival and altered morphological maturation of new-born neurons (Morris, Eaves, Smith & Nixon, 2010).

In humans, the chronic use of alcohol has been associated with hippocampal dysmorphology. Beresford et al. (2006) used MRI to examine hippocampal volumes in chronic alcohol-dependent subjects with a history of heavy drinking and light drinking non-alcohol-dependent controls. Alcohol dependent subjects with a history of heavy drinking displayed reduced total and left hippocampal volumes compared to light drinkers who were not alcohol dependent. A number of other studies have observed structural abnormalities within the hippocampus of adolescent drinkers. De Bellis et al. (2000) used MRI to compare hippocampal volumes between subjects with alcohol use disorders and healthy controls. Findings showed significantly reduced left and right hippocampal volumes in alcohol dependent participants relative to healthy controls. Reduced hippocampal volumes were found in those subjects who began using alcohol at an early age and who had been diagnosed with an alcohol use disorder for a longer period of time. Evidence from Medina, Schweinsburg, Cohen-Zion, Nagel & Tapert (2007) is consistent with these findings and suggests that adolescent drinking has a detrimental affect to the structure of the hippocampus. The authors found significant aberrations in hippocampal asymmetry and left hippocampal volumes in heavy adolescent drinkers. Interestingly, hippocampal asymmetry was related to learning abnormalities in these subjects.

The literature outlined above indicates that chronic exposure to cigarette smoking and alcohol use might give rise to the development of abnormalities within the brain. The prefrontal cortex and the hippocampus are two brain regions affected by chronic cigarette smoking and alcohol use. These findings are significant based on the understanding that these brain regions are heavily implicated in PM tasks (Burgess et al., 2003; Okuda et al., 1998; 2007).

4.5 Chapter Summary

The present Chapter has examined significant evidence that suggests that both illicit and licit drugs have the potential to damage a wide range of brain regions including frontal, medial temporal and posterior areas. Taken together, these findings might be useful in explaining observed PM deficits in substance users. Chapter 5 explores the variety of self-report and

laboratory-based measures available to researchers who want to study PM. Chapter 6 examines the research which has used these measures to investigate PM performance in illicit and licit substance users.

Chapter 5: Assessment of prospective memory

Chapter Outline

The present Chapter introduces some of the most commonly used self-report and laboratory-based measures of PM. The reliability and validity of self-report measures are discussed. Particular attention is given to measures that have previously been used in drug-related literature and to those which have been used in the empirical work of the thesis.

5.1 Self-report measures of prospective memory

The Prospective Memory Questionnaire (PMQ; Hannon et al., 1995)

The PMQ is a self-report measure of PM that provides measures of three classes of PM. These include short-term habitual PM, long-term episodic PM and internally cued PM. Each aspect of PM is measured on a scale of 1-9. Fourteen questions measure short-term habitual PM (e.g. “I forgot to lock the door when leaving my apartment or house”), while fourteen items measure long-term episodic PM (e.g. “I forgot to send a card for a birthday or anniversary”) and ten questions measure internally cued PM (e.g. “I forgot what I came in the room to get”. A further fourteen questions provide a measure of the strategies used to facilitate remembering (e.g. “I make lists of things I need to do”).

The Prospective Retrospective Memory Questionnaire (PRMQ; Crawford, Smith, Maylor, Della Sala & Logie, 2003)

The PRMQ is a self-report measure of PM that also incorporates measures of RM. Eight questions refer to PM failures (e.g. “Do you decide to do something in a few minutes time and then forget to do it?”), while a further eight investigate RM failures (e.g. “Do you fail to recognise a place you have visited before?”). Both of these components of real-world memory are measured on a 5-point Likert Scale ranging from “very often” to “never”. Participants are required to specify how often each item happens to them in everyday life. Ratings are assigned numerical values of 5 (very often) to 1 (never) in order to provide a total score for each subscale (PM and RM). Each subscale has a minimum score of 8 and maximum score of 40 where higher scores are suggestive of more memory problems. The effectiveness of these self-report instruments in measuring PM has been demonstrated across

a body of psychological research including investigations of the effects of personality (Heffernan & Ling, 2001), age (Heffernan & Elmirghani, 2000), and drug use on successful prospective remembering. Research that has used these measures to investigate the effects of substance use on PM has found evidence for alcohol (Heffernan et al., 2006) and nicotine-related (Heffernan et al., 2005) PM deficits. Although these findings demonstrate drug-related PM impairments, this report will focus primarily on the effects of ecstasy use and, to a lesser extent, the effects of cannabis use on PM.

Comprehensive Assessment of Prospective Memory (CAPM; Roche, Moody, Szabo, Fleming & Shum, 2007)

The CAPM is a 54-item questionnaire that is divided into three subcategories. Section A (CAPM/A) is compromised of 39 items and assesses frequency of PM lapses. Ten items focus on the basic activities in everyday living (e.g., "forgetting to eat a meal"). Twenty-three items focus on the instrumental activities of everyday living (e.g., "forgetting to pay a bill"). Six further items are unclassified and contribute to a CAPM/A overall score. Section B (CAPM/B) is based on the same 39-items used for calculating PM lapses in section A but this time participants are asked to indicate their degree of concern about each PM failure.

Items in section A and B are rated using a 5-point Likert scale: 1=never, 2=rarely (once/month), 3=occasionally (2-3 times/month), 4=often (once/week), 5=very often/daily, n/a=not applicable. Item responses are averaged for all items within each scale such that higher scores indicate higher PM failures (section A) and increased concern about PM failures (section B). Section C (CAPM/C) includes 15 items which concentrate on specific reasons for PM failures (e.g., "the more things (say two or three) I have to do, the more likely I will forget to do them". Participants are asked to indicate the degree to which they agree with each statement using a 4-point Likert scale: 1=strongly disagree, 2=disagree, 3=agree, and 4=strongly agree.

Time-Cued Prospective Memory Questionnaire (TCPMQ; Cuttler & Graf, 2009)

The TCPMQ is a 50-item questionnaire that is divided into three sections. The first section includes 39-items and assesses the frequency of time-cued PM failures. Participants indicate how often they forget to carry out time-based PM intentions (e.g., "I forgot to go to my dentist appointment") using a 5-point scale: 1=never, 2=seldom, 3=sometimes, 4=often,

5=very often and n/a=not applicable. Item responses are averaged across all items with higher scores indicating increased frequency of time-based PM forgetting. The second section of the questionnaire is focused on time-cued PM punctuality. Participants are presented with the same 39-items and are asked to indicate how punctual they are when performing each task. The third section is an 11-item questionnaire which measures the use of memory aiding strategies. Items concentrate on a number of memory aiding strategies including the use of post-it notes, alarms, cell phones and reminder services (e.g., "I use the alarm services on my PDA to help me remember to do things on time"). Items are scored on a 5-point Likert scale: 1=never, 2=seldom, 3=sometimes, 4=often, 5=very often and n/a=not applicable. Item responses are averaged across all 11-items with higher scores demonstrating increased use of memory aids and strategies.

5.2 Reliability and validity of self-report measures of prospective memory

A review of the literature shows that both the PMQ (Hannon et al., 1995) and the PRMQ (Crawford et al., 2003) have acceptable to very good levels of reliability but poor levels of validity (Hannon et al., 1995; Kliegel & Jäger, 2006; Mäntylä, 2003). For example, evidence for convergent validity (i.e., the degree to which two measures or constructs that should be related, are in fact related; Uttl & Kibreab, 2011) is lacking such that correlations with objective measures of PM are extremely low (PMQ; Hannon et al., 1995; PRMQ; Kliegel & Jäger, 2006; Mantyla, 2003), Nonetheless, these studies have been criticised on the basis that they have used unreliable binary measures of PM (Uttl & Kibreab, 2011). Thus, the lack of convergent validity found in previous studies may be explained by poor criterion objective measures of PM (Uttl & Kibreab, 2011). The use of more continuous measures of PM may be more useful when measuring the convergent validity of self-report measures of PM.

To test this proposal, Uttl and Kibreab (2011) developed their own continuous objective measure of PM. Participants were asked to circle presentations of a PM cue while they were working through a series of questionnaires. The PM cue was presented a total of four times in an intrusive visual form. The PM cue which was first circled was used as an indication of PM performance. Participants received four points if they circled the first PM cue and one point if they only circled the last PM cue. No points were received if participants failed to circle any of the PM cues. In order to assess convergent and divergent validity (i.e., the extent to which two measures of different constructs do not correlate with each other) of self-report measures of PM, Uttl and Kibreab (2011) asked participants to complete several

self-report measures of PM (PMQ; Hannon et al., 1995, PRMQ; Crawford et al., 2003, CAPM; Roche et al., 2007, TCPMQ; Cuttler & Graf, 2009) and RM. For a self-report measure of PM to have high convergent validity, it should have a high correlation with other self-report measures of PM. In contrast, if a self-report measure of PM has high divergent validity, it should have a low correlation with measures of other constructs (in this case, RM). The authors also examined the convergent and divergent validity of self-reports of PM against objective measures of PM. To be valid here, self-report measures of PM should have a high correlation with objective measures of PM and a low correlation with objective measures of other constructs. Despite using a newly developed, continuous measure of PM, the results showed poor convergent and divergent validity for self-report measures of PM. Overall findings within the literature demonstrate high levels of reliability but low levels of validity of self-report measures of PM.

5.3 Laboratory-based measures of prospective memory

The Call-In Prospective Memory Test (Cuttler, Graf, Pawluski & Galea, 2011)

The Call-in PM Test is a time-based PM task where participants are required to call the laboratory one week after the initial test-session. Participants select their own time window which governs when they should call the laboratory. Two points are awarded to participants who call the laboratory on the correct day and at the right time. One point is awarded to participants who call the laboratory at the incorrect time. No points are awarded if participants fail to call the laboratory.

The Cambridge Prospective Memory test (Wilson et al., 2005)

The Cambridge Prospective Memory test (CAMPROMPT) includes three measures of event-based PM and 3 measures of time-based PM. Over a 20-minute period, participants are asked to partake in some distracter tasks in the form of either a word-finder puzzle or a general knowledge quiz. Meanwhile, participants are also required to complete several PM tasks. Participants are provided with a kitchen timer for the first two time-based PM tasks. The first time-based PM task requires participants to remind the experimenter to remember an item (e.g. a mug, keys) 7-minutes before the end of the scheduled 20-minute period. When the timer displays 16-minutes, the participant receives a reminder that they need to stop whatever task they are doing and move to another “in 7-minutes time”. This is the second time-based

PM task. The final time-based is governed by a wall-clock where the participant is given a specific time (e.g. 5-minutes after the test-session is complete) at which they need to remind the experimenter to ring the garage/reception.

The first event-based task concerns the general knowledge quiz and involves the participant returning a book to the experimenter following the presentation of a question on the television series, “Eastenders”. The second event-based task requires the participant to return an envelope labelled “MESSAGE” to the experimenter following the receipt of a reminder that there are only 5-minutes left until the end of the test-session. After being informed that the test-session is complete, participants are asked to remind the experimenter of the location of 5 items that were hidden at the start of the test-session. The maximum score for each of the six subtasks is six. A score of six is given if the task is completed without the need for a prompt from the experimenter. Four points are awarded if the task is completed successfully following the receipt of a single prompt from the experimenter. Thereafter, participants are awarded two points if the task is completed upon the receipt of a second prompt, one point if prompting is received but the task is only completed at the second attempt and no points if after prompting, the task has not been completed successfully. A total score for time-based PM and event-based PM is then calculated based on a maximum score of 18 for each. Higher scores represent superior performance on each of these PM measures.

The Karolinska fatigue PM task (Hadjiefthyvoulou et al., 2011a)

The Karolinska fatigue PM Task is a medium-term measure of time-based PM. Upon entering the laboratory, participants are asked indicate their current level of fatigue on the “Karolinska Sleepiness Scale” (see Gillberg et al., 1994). Participants are asked to provide an indication of their fatigue every 20-minutes, up until the end of the test-session. Participants receive two scores as percentages based on the number of times that they remember to complete the scale during the first and second halves of the test-session. Participants who forget to complete a questionnaire receive a prompt from the experimenter.

The Fruit Prospective Memory Task (Cuttler et al., 2011)

Participants are instructed that they will see pictures of fruit at some time during the test-session. Upon presentation of the fruit, participants are required to stop what they are doing and press the “p” key on a computer keyboard. A total of four pictures are presented during

the test-session and participants receive one point for each correct prospective response that is made.

The JAAM assessment (Jansari, Agnew, Akesson & Murphy, 2004)

The JAAM assessment is a virtual reality assessment whereby participants take the role of someone working in an office environment helping to set up a meeting. Participants are given a scenario to read which describes the virtual environment and their role for the task. Participants are instructed and shown how to navigate around the virtual environment. Participants are provided with a list of tasks that need to be completed for their "office manager" (e.g., arranging for items of post to be collected, setting up tables and chairs for a meeting, turning on the coffee machine when the first person arrives for the meeting). Further to the tasks that participants are aware of at the beginning of the task, they are also given a number of memos during the experiment which require them to perform additional tasks or amend a current task.

The JAAM assessment consists of eight subscales: The *Planning* subscale requires participants to order items in a logical manner rather than their perceived importance. As such, participants have to identify the tasks that should logically be carried out first. The *Prioritisation* subscale requires participants to order items according to their relative importance. This requires participants to order the most important items first and the less important items last. The *Selection* subscale requires participants to choose between two or more tasks by deciding which of the tasks is most important. For example, the participant has a number of items of post that need to be sent to different locations and with differing levels of urgency. Participants must therefore select the appropriate postal service to collect the letters and parcels based on their relative urgencies and locations. The *Creative Thinking* subscale requires participants to solve a number of problems. Participants must find their own solutions to the problems. In one case, participants are required to find a way to cover up some graffiti which has been written in permanent ink. The *Adaptive thinking* subscale tests participant's ability to put forward suitable solutions to new problems as they arise.

The three remaining subscales measure PM. The *Action-based prospective memory* subscale requires participants to execute a task/action cued by a stimulus in the task they are already engaged with. For example, when participants receive a message about new items of post that

need to be sent, they must update the post diary accordingly. In the *Event-based prospective memory* subscale, participants must remember to execute an event-based PM task. For example, participants are asked to note the specific time of the fire alarms on their notes for the manager. In the *Time-based prospective memory* subscale, participants must remember to perform a time-based PM task. For example, participants are asked to turn on the overhead projector 10 min before the start of the meeting. Participants are given a rating of 0 (no attempt made), 1 (satisfactory performance) or 2 (perfect performance) for each subscale of each construct. Participants are given a total score as a percentage by summing the raw scores for each subscale, dividing by the total possible score and multiplying by 100.

The long-term delayed recall task (Hadjiefthyvoulou et al., 2011a)

This task is based on a paradigm developed by Einstein et al. (1995) and Mathias and Mansfield (2005). The Rey Auditory Verbal Learning Task (RAVLT) is amended to provide a long-term measure of PM. The RAVLT consists of two lists of 15 words that the researcher reads to each participant. For 5 consecutive trials, the researcher reads the list to the participant who is then asked to recall as many words as possible. Following the fifth trial, the researcher reads a separate list of 15 words to the participant. This is called the interference trial. Upon completing the interference trial, the participant is asked to write down as many words from the first word list without hearing the list again. Twenty-minutes later, the participant is asked to write down as many words from the first list as possible. This is the seventh trial. The prospective component of this task involves the participant being asked to write down as many words as they can recall from the first list, one, two, and three weeks after the time of testing. Each time, the participant is asked to date their response sheet and to return it to the experimenter in an envelope provided for them. Participants receive a score out of three based on the number of delayed recall test sheets returned. Higher scores are indicative of better PM performance.

The Memory for Intentions Screening Test (Raskin, Buckheit, & Sherrod, 2010)

The Memory for Intentions Screening Test is a 30-minute laboratory-based measure of PM which is compromised of four, two-minute trials (e.g., “When I hand you a request for records form, write your doctors’ names on it”) and four 15-minute trials (e.g., “In 15 minutes, use that paper to write the number of medications you are currently taking”) during which the participant is engaged in an ongoing distractor task (i.e., a standardised word

search). Both sets of trials (two-minute and 15-minute trials) are balanced on time- and event-based cues and all cues are non-focal. Responses are scored on a scale of 0–2 for each item, such that scores for the two-minute and 15-minute trials range from 0–8. Higher scores are indicative of better PM performance

The F1 event-based PM task (Hadjiefthyvoulou et al., 2011a)

The F1 event-based PM task is based on Fisk and Warr's (1996) processing speed task. However, recent amendments have included the addition of an event-based measure of PM. Firstly participants are presented with two patterns; one located at the top; and one located at the bottom of a computer screen. The participant is then required to indicate whether they believe the two patterns are the same or different. The "same" responses are programmed to the "/" key on a keyboard and the "different" responses are programmed to the "z" key on a keyboard.

In an event-based PM component, participants are also required to press the "F1" key following the presentation of the words "Please wait a moment" in the top left hand corner of the computer screen. Participants are informed that this will store their responses in the memory of the computer. In the event that a participant does not press "F1", their scores are reported as "errors". In total, this task is completed three times, in each case at three levels of complexity, and a final event-based PM score is calculated based upon the number of times that a participant forgets to press the "F1" key.

The Real World Prospective Memory Task (Heffernan, O'Neill & Moss, 2012)

The Real World PM Task is a measure of objective everyday PM. Participants are presented with a list of 15 specific locations around a university campus (e.g., "when you reach the Students Union"), accompanied by a list of associated actions (e.g., "Ask if there is a job available"). The participant is given 1.5 min to memorise the list before receiving a short tour of the university. Participants are required to verbally recall both the location and the associated action, but only when they reached a location that was on the original list. The order of the location-action pairings on the tour are different to the order of the location-action pairings on the original list.

A number of non-target locations that are not included on the original list are also included which act as non-target distracter locations (e.g., passing a coffee shop on campus).

Interruptions are included whereby the participant engages in a conversation with the researcher about everyday university life. One point is given for each location–action combination correctly recalled. Scores range from 0 to 15 with the higher score indicating better PM performance.

The Rivermead Behavioural Memory Test- Extended Version (RBMT; Wilson et al., 1985)

The RBMT consists of 8 subtasks relating to aspects of everyday memory functioning. The PM components of the RBMT consist of three subtasks. The *Belonging* subtask provides a measure of event-based PM. At the start of the test-session, the experimenter hides an object (e.g. a pen) in a specific location (e.g. on a shelf). The participant is required to remind the experimenter of the object and its location at the end of the test-session. A maximum score of two is awarded if the object and its location are correctly recalled. A score of one is awarded if the object and its location are correctly recalled after the receipt of a prompt. A score of zero is awarded if the object and its location are not recalled.

The *Appointment* subtask provides a measure of time-based PM. An alarm is set for a period of 20-minutes. The participant is required to ask a predefined question at the end of the 20-minute period. A score of two is awarded if the question is recalled without the receipt of a prompt. A score of one is awarded if the question is asked following the receipt of a prompt. A score of zero is awarded if the participant does not recall the question.

The *message* subtask provides a measure of event-based PM. The experimenter demonstrates a *Route*, consisting of five sections, to the participant depositing a message at a specific location on the way. Participants are required to replicate the *Route* whilst depositing the *message* at the correct location. This task is completed immediately after the initial observation and after a delay. A maximum score of three is awarded if no errors are made during the two attempts. Scores then gradually decrease according to the total number of errors made during both attempts. The minimum score for this task is zero.

The Reminder Prospective Memory Task (Cuttler & Graf, 2009)

Participants are asked to give the experimenter a reminder once they have completed a number of cognitive tasks. Participants are provided with details relating to the final

cognitive task that they will complete. However, motivation to carry out the PM intention is manipulated in two conditions; high motivation and low motivation. In a high motivation condition, participants are asked to remind the experimenter to award them with their participant research credits. In a low motivation condition, participants are asked to remind the experimenter to email their supervisor. Two points are awarded if participants give the reminder at the correct time. One point is awarded if participants give the reminder at the incorrect time. No points are awarded if participants fail to give the reminder.

The Video-based prospective memory task (Bartholomew, Holroyd & Heffernan, 2010)

The video-based PM task is based on a modified version of a paradigm developed by Titov and Knight (2001). Participants are presented with a list of 17 specific locations (e.g., "at HMV") and associated actions. Participants are required to carry out a task (e.g., "buy a CD") or answer a question about something at the location (e.g., "what colour is that stall's canopy?") upon presentation of location cues. During the task itself, participants are presented with a 10-minute video depicting a shopping area. Shop fronts and passers-by provide location cues where participants should then recall location–action combinations. Participants are given a total score between 0 and 17 depending on the number of location-action pairings correctly recalled. One point is awarded for every location–action combination correctly recalled. Participants receive no points if only one member of the pair is correctly identified.

The Virtual Week task (Rendell & Craik, 2000)

The Virtual Week is a laboratory based task that aims to capture features of real-life PM tasks by including recurring PM tasks, non-recurring PM tasks, event-based PM tasks and time-based PM tasks. The Virtual Week itself is a board game where players move around a board via the roll of a dice. Several times of day where people are most likely to be awake are listed at various points around the board. Each circuit of the board that a player completes constitutes one "day" in the game. Each "day" contains 10 PM tasks; 4 "regular" PM tasks; 4 "irregular" PM tasks; and 2 time-checks.

The regular tasks are made up of two event-based PM tasks where participants are instructed to take some antibiotics with breakfast and dinner, and two time-based PM tasks where

participants are required to take asthma medication at 11 a.m and 9 p.m. In the two time-check tasks, a stop-clock is started at the beginning of each circuit of the board and participants are required to complete two lung tests, at 2-minutes 30 seconds and at 4-minutes and 15 seconds. Importantly, these times are different to the times which are listed on the board. The two time-check tasks serve to provide a "breaking set" from the board game activity. Players must move around the board seven times to complete the "Virtual Week" (see Rendell et al., 2007).

5.4 Chapter summary

The PMQ and The PRMQ are two self-report measures which have been used to investigate the effects of illicit drugs on PM (see Cuttler et al., 2012; Fisk & Montgomery, 2008; Heffernan, Clark, Bartholomew & Stephens, 2010a). However, the validity of each of these measures is questionable (PMQ; Hannon et al., 1995; Uttl & Kibreab, 2011; PRMQ; Kliegel & Jäger, 2006; Mäntylä, 2003; Uttl & Kibreab, 2011) and this has given rise to the increased use of laboratory-based measures in many studies. Laboratory-based measures provide researchers with a more objective way of investigating PM deficits across samples. The Virtual Week task (Rendell & Craik, 2000), the F1 event-based PM task (Hadjiefthyvoulou et al., 2011a), the long-term delayed recall PM task (Hadjiefthyvoulou et al., 2011a), the fatigue PM task (Hadjiefthyvoulou et al., 2011a) and the CAMPROMPT (Wilson et al., 2005) are among the laboratory-based PM measures commonly used in drug-related research. This literature is discussed at length in Chapter 6.

Chapter 6: The effects of licit and illicit drugs on prospective memory

Chapter overview

The present Chapter outlines the literature which has investigated the effects of licit and illicit drugs on PM. PM deficits in cannabis, ecstasy, cocaine, tobacco and alcohol users are examined. The extent to which drug users exhibit deficits in event- and or time-based PM are discussed. For the purpose of the empirical work in this thesis, particular attention is given to the effects of ecstasy/polydrug use on PM.

6.1 Prospective memory deficits in cannabis users

Findings from studies investigating the self-reported PM problems in cannabis users have been inconsistent with some studies showing a significant correlation between cannabis use and PM deficits (Cuttler et al., 2012; Fisk & Montgomery, 2008; Rodgers et al., 2001; Montgomery & Fisk, 2007) and other studies failing to demonstrate this effect (Bartholomew et al., 2010; Rodgers et al., 2003).

Some studies have shown cannabis-related impairments on specific subscales of the PMQ (episodic and internally cued PM, Cuttler et al., 2012, Study 1; short-term and internally-cued PM, Rodgers et al., 2001) while other studies demonstrate clear cannabis-related impairments on all subscales of this measure (short-term habitual; long-term episodic; and internally cued PM; Fisk and Montgomery, 2008). Further inconsistencies are found in recent data which has shown no significant differences between cannabis users and non-users on any of the PM subscales of the PMQ (Bartholomew et al., 2010). However, the somewhat equivocal findings are accompanied by a large variance in the ages of cannabis users across studies. For example, the sample of cannabis users in Bartholomew and colleague's (2010) study were younger (median=19) than cannabis users in Cuttler et al's (2012; mean=20.75) Fisk and Montgomery's (2008; mean=21) and Rodgers et al's (2001; modal age group=21-25) research. Thus, relative to the cannabis users in Bartholomew and colleague's (2010) study , it is possible that the cannabis users in the latter three studies had been using cannabis for an extended period of time. Ultimately, this may reflect a higher total lifetime exposure to cannabis, perhaps explaining why increased cannabis-related deficits in PM have been observed in cannabis users in some studies (Fisk & Montgomery, 2008; Rodgers et al., 2001).

Laboratory-based measures of PM have highlighted PM deficits in cannabis users. However, findings in the literature have, once again been inconclusive with some studies showing clear cannabis-related PM deficits on objective PM measures (Hadjiefthyvoulou et al., 2011a; Hadjiefthyvoulou et al., 2011b; McHale & Hunt, 2008) and others showing no evidence of an impairment (Cuttler et al., 2012; Study 2). In one study, McHale and Hunt (2008) used the RBMT and found significant short-term and long-term time-based PM impairment in chronic cannabis users. In contrast, there was no evidence of event-based PM deficits in chronic cannabis users (*Message* Subset). This finding is not consistent with Hadjiefthyvoulou et al. (2011a) who also used the RBMT and found that frequency of cannabis use was associated with unique variance on both, the event-based, *Message* subset of the RBMT and the time-based, long-term recall PM task among ecstasy/polydrug users. Specifically, increased frequency of cannabis use was associated with poorer performance on both PM measures.

In another study from the same laboratory, Hadjiefthyvoulou and colleagues (2011b) used the CAMPROMPT to investigate drug-related deficits in PM. One advantage of the CAMPROMPT over other laboratory-based measures of PM is that it is more sensitive to individual differences in both clinical and normal populations (Hadjiefthyvoulou et al., 2011b). Overall, there were no differences between cannabis-only users and non-illicit drug users on event- and time-based PM subtasks of the CAMPROMPT (Hadjiefthyvoulou et al., 2011b). However, increased levels of cannabis consumption in the 30 days leading up to the test-session and increased frequency of cannabis use were associated with inferior performance on event-based PM tasks in ecstasy/polydrug users.

A more recent study that used three self-report PM measures (PMQ, PRMQ, TCPMQ) and three objective PM measures (Fruit PM test, Reminder PM test, Call-in PM test) failed to find clear cannabis-related impairments in PM (Cuttler et al., 2012; Study 2). For example, chronic cannabis users (people who has used cannabis three times a week for a year or more) only reported significantly more PM failures compared to experimental cannabis users (people who had used cannabis five or fewer times in their lifetime) and non-drug users on one subscale of the PMQ (internally cued PM). Furthermore, this impairment dropped to below statistical significance after controlling for RM processes. In addition, chronic cannabis users showed no impairment on any of the objective PM measures compared to experimental cannabis users and nonusers. These findings do not support

previous research which has demonstrated cannabis-related impairment on laboratory-based measures of PM (McHale & Hunt, 2008; Hadjiefthyvoulou et al., 2011a; Hadjiefthyvoulou et al., 2011b). One possible reason for this difference may concern the laboratory-based PM tasks that were used in Cutller et al's (2012) study. Cuttler and colleagues (2012) acknowledge that their laboratory-based PM measures lack sensitivity in detecting problems in PM. This is because none of the three laboratory-based measures that were used contain a large number of PM trails. Thus, detecting any PM problems which may have been evident among the chronic cannabis users or the experimental cannabis users was difficult. It is also interesting to note that subjective PM performance was mediated by RM processes (Cuttler et al., 2012; Study 1 and Study 2). Cuttler et al. (2012) note they deliberately used laboratory-based PM measures which placed minimal demands on RM. If PM performance is in fact underpinned by RM, it is not surprising that the authors failed to detect cannabis-related deficits on the laboratory-based measures.

A number of self-report (Cuttler et al., 2012; Fisk & Montgomery, 2008; Rodgers et al., 2001; Montgomery & Fisk, 2007) and laboratory-based measures (McHale & Hunt, 2008; Hadjiefthyvoulou et al., 2011a; Hadjiefthyvoulou et al., 2011b) have demonstrated PM impairment in cannabis users. Total cannabis consumption and frequency of cannabis use may mediate the extent to which cannabis users display PM deficits. This appears to be especially true for ecstasy/polydrug users (Hadjiefthyvoulou et al., 2011a; 2011b).

6.2 Prospective memory deficits in ecstasy users

In one of the primary investigations of the effects of ecstasy use on self-perceived PM deficits, Heffernan, Ling and Scholey (2001a) found increased reports of PM errors in ecstasy users compared to non-users. While these self-reported deficits were consistent across the three PM subscales measured by the PMQ (short-term habitual PM; long-term episodic PM; internally cued PM), ecstasy users and non-users did not differ significantly in terms of the strategies used to aid PM remembering. Importantly, these group differences were still evident even after controlling for covariates such as other drug use. Although these findings were supported in a second paper (Heffernan, Jarvis, Rodgers, Scholey & Ling, 2001b), more recent research has not been consistent (Montgomery & Fisk, 2007). Montgomery and Fisk (2007) found cannabis use to be a significant predictor of PM errors in ecstasy users on the short-term habitual, long-term episodic and internally cued PM subscales of the PMQ.

However, the increased reports of lifetime cannabis use reported in this study (Montgomery & Fisk, 2007) compared to previous investigations (Heffernan et al., 2001a; 2001b) may explain the different findings.

The laboratory-based PM data is generally consistent with self-report data in showing clear ecstasy-related impairments in PM. In one of the first investigations to administer a laboratory-based measure of PM to illicit drug users, Rendell et al. (2007) found evidence of PM impairment in both "frequent" and "infrequent" ecstasy users on The "Virtual Week" task. In stark contrast to cannabis users (McHale and Hunt, 2008), both "frequent" and "infrequent" ecstasy users displayed deficits in both event- and time-based PM. Nevertheless, event- and time-based PM deficits were attenuated among "infrequent" ecstasy users (Rendell et al., 2007) suggesting that there may be a lifetime dose-related effect of ecstasy use on PM impairment. Interestingly, former users of ecstasy also exhibit event- and time-based impairments in PM on the "Virtual Week" task highlighting the potential long-term deficits resulting from MDMA exposure (Rendell, Mazur & Henry, 2009). Despite these findings, the use of The "Virtual Week" task as an objective PM measure has been criticised on several grounds. Hadjiefthyvoulou and colleagues (2011a) argue that successful performance on The "Virtual Week" task is highly dependent on components of associative learning. For example, prior to the completion of the PM task components, participants must ensure that they are aware of specific responses/behaviours that are paired to different locations on the board. Given that ecstasy users display impairments in paired associative learning (Gallagher et al., 2012; Montgomery et al., 2005), it is possible that poor PM performance observed on The "Virtual Week" task reflects a deficit in associative learning rather than PM itself.

In light of the potential limitations of The "Virtual Week" paradigm, a number of studies have used alternative measures of PM. Zakzanis, Young and Campbell (2003) used the RBMT and found that abstinent ecstasy users made significantly more PM errors than non-users on both event- (*Message)* and time-based (*Appointment)* subsets of the measure. These findings have not been supported by more recent research which has used the RBMT (Hadjiefthvouolou et al., 2011a). Hadjiefthyvoulou and colleagues found that ecstasy users performed similarly to non users on the time-based *Appointment* and event-based *Message* subsets of the RBMT but significantly worse than non users on the time-based *Belonging* subset.

Other event-and time-based measures of PM that were used in Hadjiefthyvoulou et al's (2011a) investigation included The F1 event-based PM task, The long-term recall PM test and the Karolinska fatigue PM task. In terms of event-based PM performance, ecstasy users exhibited more problems than non-users in remembering to press "F1" during the F1 event-based PM task. Ecstasy/polydrug users were two to three times more likely than non-users to forget to press "F1" on the F1 event-based PM task.

In relation to short-term time-based PM performance, ecstasy/polydrug users had particular difficulty in completing the Karolinska fatigue PM task, especially during the final half of the experiment. Ecstasy/polydrug users only remembered to complete 51% of the fatigue questionnaires that were completed by non-users. With regard to more long-term time-based performance, non-users posted back significantly more delayed recall response sheets than ecstasy users during the 3 week period that followed the initial test-session (long-term delayed recall PM task). Importantly, the evidence from this study is indicative of ecstasy-related impairments on event-based PM tasks as well as short-term and more long-term measures of time-based PM. Findings from this study suggest that ecstasy use induces a globalised deficit in PM. Importantly, the observed group effects remained statistically significant after controlling for several covariates including frequency of cannabis use, total lifetime cannabis use, and current alcohol and tobacco intake. Further analyses of RM and executive functioning (EF) suggested that ecstasy/polydrug-related deficits in PM were not attributable to group differences in these memory processes. These findings increase the likelihood that the PM deficits found among ecstasy/polydrug users can be attributed to the use of ecstasy rather than the use of other illicit drug use or deficits in other aspects of memory.

A further study by Hadjiefthyvoulou and colleagues (2011b) used the sensitive CAMPROMPT measure to investigate differences in PM functioning between ecstasy/polydrug users, cannabis only users and non-illicit drug users. Measures of RM and EF were included to establish whether any observed ecstasy/polydrug-related impairments in PM were attributable to group differences in these processes. Findings showed that ecstasy users performed significantly worse than both cannabis only users and non illicit drug users on event-based subtasks of the CAMPROMPT. Ecstasy users were also significantly impaired on the time-based subtasks on the CAMPROMPT compared to non illicit drug users. Although better RM and EF performance was associated with improved PM

performance, this trend only approached statistical significance and did not underpin the PM impairments that were observed.

While Hadjiefthyvoulou and colleagues (2011a; 2011b) found substantial evidence for a globalised PM deficit among ecstasy/polydrug users, evidence from other studies are inconsistent. Weinborn, Woods, Nulsen and Park (2011) used the Memory for Intention Screening Test and found that ecstasy users were significantly impaired on long-term PM tasks (15-minute delay intervals) compared to high-risk alcohol users and non illicit drug users. This effect was particularly apparent for time-based PM tasks. No group differences were found for short-term PM tasks (2-minute delay intervals). RM and executive functions were not associated with long-term PM performance in ecstasy users confirming findings from previous research (Hadjiefthyvoulou et al., 2011a; 2011b). Long-term PM impairment in ecstasy users was attributed to risky decision making behaviour. From a multiprocess perspective (McDaniel & Einstein, 2000), it is feasible that ecstasy users have particular difficulty in strategic target monitoring over longer delay periods and that this deficit is accentuated in time-based PM tasks. In other words, ecstasy users may be less able to maintain cue-action pairings over longer delay periods compared to non illicit drug users.

The absence of short-term PM deficits in ecstasy users in this study might be explained by the low levels of lifetime ecstasy use. For example, the ecstasy users sampled in Weinborn et al's (2011) investigation had a relatively low level of lifetime consumption (mean=56.5 tablets) compared to other studies where short-term PM deficits have been found (Hadjiefthyvoulou et al., 2011a, mean=668.90; Hadjiefthyvoulou et al., 2011b, mean=640.90). This is crucial considering that there is an association between lifetime ecstasy use and cognitive performance (Bedi & Redman, 2008).

6.3 Prospective memory deficits in cocaine users

Until recently, there has been a lack of evidence to suggest that cocaine use has detrimental effects to PM performance. However, two recent studies have found a relationship between cocaine use and PM (Hadjiefthyvoulou et al., 2011a; 2011b). In one study, Hadjiefthyvoulou et al. (2011a) found that lifetime cocaine use correlated with performance on the *Appointment* and *Belonging* subscales of the RBMT, the Karolinska fatigue PM task and the long-term delayed recall PM task in a group of ecstasy/polydrug users. Performance on these PM measures decreased as lifetime use of cocaine increased. Frequency of cocaine use was also

associated with performance on the *Appointment* and *Belonging* subscales of the RBMT task, the Karolinska fatigue PM task, the F1 event-based PM task and the long-term delayed recall PM task. Increased frequency of cocaine use was associated with worse performance in all cases. Although the polydrug user group was primarily identified by ecstasy use, cocaine use was clearly implicated in the event-and time-based PM deficits that were found._These findings were confirmed in another study from the same laboratory which found a clear relationship between cocaine use and event-based PM performance on the CAMPROMPT (Hadjiefthyvoulou et al., 2011b). Specifically, increased lifetime dose, greater consumption in the last 30 days and increased frequency of use were all associated with poorer event-based PM performance on the CAMPROMPT.

Hadjiefthvouolou et al. (2011b) propose that PM deficits in cocaine users may stem from disruptions within the dopaminergic system. For example, exposure to cocaine has been linked to dysfunction of the dopaminegic system in PM-related brain regions such as the prefrontal cortex (Tomasi et al., 2007). Furthermore, the specific dopaminergic systems which are suggested to be affected by cocaine use play an important role in EF processes. This is significant given the potential role of EF in PM processes (Kopp & Thöne-Otto, 2003; Heffernan & Bellis, 2012; Martin et al., 2003). Thus, abnormalities within the dopaminergic systems involved in executive functions may explain the negative association between cocaine use and PM functioning.

PM deficits that have been observed in Parkinson's patients (Kliegel et al., 2005) are also significant given that the disease is associated with impairment to dopaminergic functioning in the corticostriatal pathway (Hadjiefthyvoulou et al., 2011b). The mesocortical dopaminergic system has an important function in PM processes (Goto & Grace, 2008) and in line with this association, administration of L-dopa improves PM performance in Parkinson's patients (Costa et al., 2008). Thus, abnormalities which have been found in the dopaminergic system of cocaine users (Ziegler, Lipton, Toga & Ellison, 1991; Tomasi et al., 2007) may be at the heart of cocaine-related impairments in PM.

Alternatively, cocaine-related deficits in PM may stem from medial temporal (Matochik et al., 2003; Sim et al., 2007) and hippocampal impairments (Tomasi et al., 2007; Zeigler et al., 1991). This proposal is consistent with findings which have found cocaine-related impairment on the RAVLT (Fox, Jackson & Sinha, 2009). Cocaine users recalled fewer

correct responses on the RAVLT compared to controls. Cocaine-related deficits on the RAVLT were related to self-reported stress levels and elevated early morning cortisol levels. Importantly, stress-related increases in cortisol levels and the associated cognitive impairments were attributed to hippocampal damage resulting from cocaine use. Thus, it is feasible that the recall aspect of PM performance may be particularly susceptible to the effects of cocaine use. This might explain the association between cocaine use and PM found by Hadjiefthyvoulou et al. (2011a; 2011b).

6.4 Prospective memory deficits in tobacco and alcohol users

Only a handful of studies have focused on the impact of persistent tobacco smoking on PM. After controlling for other drug use, Heffernan et al. (2005) found that regular tobacco smokers reported significantly more everyday PM lapses on the PMQ compared to people who had never smoked. A later study by Heffernan, O'Neill and Moss (2010b) aimed to further investigate PM deficits in tobacco smokers by using an alternative self-report measure of PM (PRMQ) and a laboratory-based measure of PM (CAMPROMPT). No difference was found on the PRMQ between existing smokers and people who had never smoked. This finding is not consistent with previous research which used the PMQ (Heffernan et al., 2005) Differences in the sample size (40; Heffernan et al., 2005 and 763; Heffernan et al., 2010b) across these studies may explain the difference in the findings. For example, it is feasible that the Heffernan et al. (2010b) study did not have sufficient power to identify different characteristics by small effect sizes. A subsequent study from the same laboratory (Heffernan & O'Neill, 2011) aimed to investigate the extent to which different subgroups of tobacco smokers (regular smokers vs. social smokers) differ in their PM abilities. In doing so, the authors were able to test to see whether there is a dose-response relationship between smoking and PM. Twenty-eight regular smokers (daily), 28 social smokers (weekend) and 28 non-smokers were compared on The Video-based PM task (see Bartholomew et al., 2010). Non smokers performed significantly better than regular smokers and social smokers on the objective PM task while no differences were observed between regular smokers and social smokers. These findings indicate that tobacco smokers are impaired on objective PM tasks but this effect is relatively independent of smoking patterns. Heffernan and O'Neill (2011) concluded that tobacco smoking does impair PM performance but not in a dose-dependent fashion.

Most recently, Heffernan et al. (2012) investigated smoking-related PM impairments in a sample of current smokers (*n*=27), previous smokers (*n*=18) and people who had never smoked (*n*=24) using The Real-World PM task. The use of The Real-World PM Task and the inclusion of a sample of previous smokers allowed the authors to determine whether objective PM deficits in tobacco smokers extend to the real world and if this deficit continues once a person stops smoking. Findings showed that existing smokers were significantly impaired in The Real-World PM Task compared to both previous smokers and non smokers. This finding might be indicative of possible PM improvement once a person has stopped smoking. However, before making definitive conclusions regarding these findings, the authors acknowledge the importance of using longitudinal designs which study PM in cohorts of people who move from a period of tobacco smoking to a period of abstinence.

Findings which have shown clear PM-related deficits in tobacco smokers (Heffernan et al., 2005, 2010b, 2011; 2012) are indicative of damage to mechanisms known to influence PM. For example, PM is highly dependent on the functioning of the prefrontal cortex (Burgess et al., 2003; Simons et al., 2006) and the hippocampus (Kliegel et al., 2008; Martin et al., 2007; Okuda et al., 1998) and thus, it is interesting to note that chronic smoking has been associated with cerebral degeneration (Nooyens, van Gelder & Verschuren. 2008; Sabia Marmot, Dufouil & Singh-Manoux, 2008). It is plausible to suggest that that persistent smoking may cause damage to the structure or functioning of PM-related brain regions which in turn hinder PM functioning (see Heffernan et al., 2012).

As with tobacco use, heavy alcohol consumption has been linked to PM impairment. In a study which investigated subjective ratings of PM deficits using the PMQ, chronic alcohol users (i.e., participants who had consumed above the recommended weekly number of units (twenty-eight units for males and 21 units for females) for a period of five years or more) reported significantly more difficulties in their PM abilities (long-term episodic PM, short-term habitual PM and internally cued PM) compared to low dose/alcohol free participants (i.e., participants who had consumed less than the recommended weekly number of units for a period of five years or more; Heffernan, Moss & Ling, 2002).

Further studies which have focused on samples of teenage cohorts indicate that excessive drinking among teenagers is associated with self-reported short- and long-term everyday lapses (Heffernan et al., 2006). Importantly, these studies controlled for the use of

other drugs known to affect PM performance (i.e., cannabis and ecstasy). In furthering the understanding of PM deficits in teenage drinkers, Heffernan et al. (2010a) found that teenage binge drinkers (i.e., participants who drank above eight units for males and six units for females on two or more occasions per week) and non-binge drinkers (average alcohol consumption=4.08 units per week) reported similar levels of PM lapses on the PRMQ. However, teenage binge drinkers performed significantly worse than non-binge drinkers on a laboratory based PM measure. After controlling for tobacco, cannabis and ecstasy use, teenage binge drinkers recalled significantly fewer location-action pairings compared to non-binge drinkers on a video-based PM task (see Chapter 5.2). Thus, while binge drinkers did not perceive themselves to have PM deficits they did display clear impairments on an objective measure of PM. These findings indicate that PM impairment in teenage drinkers may relate to specific drinking patterns.

More recent research has further highlighted the problematic effect of alcohol on prospective remembering. Griffiths et al. (2012) used the "Virtual Week" task to investigate objective PM performance in alcohol dependent persons. Twenty-four abstinent individuals with alcohol dependence and 24 social drinkers were matched on age, gender and years of education and performance was compared on the "Virtual Week" task. Alcohol dependent participants demonstrated significantly poorer event-based PM performance compared to social drinkers. Impairments were linked to ineffective application of strategies to aid the detection of PM cues.

Time-based PM impairments have also been found in binge drinkers. Heffernan and O'Neill (2012) compared self-reported PM performance (PRMQ) and objective PM performance (CAMPROMPT) in young adult binge drinkers and non-binge drinkers. No differences were found in the self-reported PM performance between the groups. However, young adult binge drinkers performed significantly worse than non-binge drinkers on time-based PM subtasks of the PMQ.

While PM deficits have been found in young adult binge drinkers and in individuals with alcohol dependence, research has investigated whether the implementation of PM strategies may enhance prospective remembering in these cohorts. For example, the use of imagery during encoding has been shown to overcome PM deficits that are commonly found after acute alcohol administration (Paraskevaides et al., 2010). The authors suggest that

vividly imagining a future intention during encoding encourages explicit engagement in future event simulation. However, recent data from Griffiths et al. (2012) suggests the employment of imagery techniques during encoding does not improve PM performance in currently abstinent alcohol dependent participants. They explain that alcohol dependent participants do not differ from social drinkers in the range of imagery skills available to them but rather fail to use them strategically. For example, social drinkers may be better able to produce detailed future event simulations by adding additional information (i.e., a specific event or time) to an intention whilst they are engaged in imagining.

Relatively little is understood about the mechanisms which might underpin PM impairments in heavy alcohol users. One proposal is that heavy alcohol use causes structural damage in the brain (Heffernan et al., 2010a). For example, excessive drinking at an early age may interfere with the structural development of the brain (Giedd, 2004; Gogtay et al., 2004). Medina et al. (2007) found aberrations in hippocampal asymmetry and left hippocampal volumes in adolescent heavy drinkers. This is pertinent in light of evidence that PM is dependent on hippocampal structures (Kliegel et al., 2008; Martin et al., 2007; Okuda et al., 1998). In addition, excessive alcohol consumption damages cerebral white matter which is crucial in binding structures together in the brain, including in PM-related regions such as the frontal and limbic systems (Oscar-Berman & Marinkovic, 2007). An alternative hypothesis might be that excessive alcohol consumption leads to reduced or abnormal levels of neurotransmitters such as 5-HT which is known to be important for mnemonic processes (Hunter, 2000; Spoont, 1992).

6.5 Chapter Summary

This Chapter has reviewed a wide body of literature that has investigated drug-related deficits in PM. PM impairments have been found in both illicit (cannabis, ecstasy and cocaine users) and licit (cigarette smokers and alcohol users) substance users. The remaining Chapters of this thesis concentrate primarily on the effects of ecstasy use on PM performance. One key aspect of ecstasy-related deficits in PM which remains to be thoroughly explored is the extent to which the typical size of ecstasy dose per session might affect PM performance. The initial empirical work discussed in Chapter 7 investigates the extent to which long-term average dose per session (typical number of ecstasy tablets taken per session averaged over number of years where an individual used the drug) and average dose per session over the last 12 months (typical number of ecstasy tablets taken per session averaged over the previous 12

months) affects PM performance. The empirical work discussed in Chapter 8 focuses on patterns of ecstasy use in the context of other drug consumption and explores the extent to which concurrent alcohol and ecstasy use may impair PM performance, respectively. Chapter 10 investigates the extent to which executive functioning deficits might underpin PM impairments in ecstasy users. Chapter 11 uses correlational analyses to investigate the relationship between long- and short-term indices of drug use and PM performance in ecstasy/polydrug users (who are identified primarily by their ecstasy use). Partial correlations are then performed to examine significant relationships while controlling for short-term effects of drug use and factors of other drug use.

Chapter 7 The effects of both long- (Study 1) and short-term (Study 2) average dose of ecstasy per session on prospective memory performance

Chapter 7 explores the effects of long- (Study 1; average typical dose of ecstasy per session averaged over the entire period of use) and short-term dose (Study 2; average typical dose of ecstasy per session over the previous 12 months) of ecstasy per session on Prospective Memory (PM) performance. Median splits were used to dichotomise long- and short-term dose of ecstasy use per session and in each case two ecstasy user groups (high dose and low dose) were created. A control group of non-ecstasy users were included in the analyses of Study 1 and Study 2. Groups were compared on a range of laboratory-based PM tasks including the F1 event-based PM task, the Karolinska fatigue PM task and the long-term delayed recall PM task. Specifically, Study 1 investigates the extent to which long-term average dose of ecstasy per session can predict PM performance. In contrast, Study 2 explores the extent to which short-term average dose of ecstasy per session is associated with PM deficits.

7.1 Introduction

Previous studies have found clear evidence of prospective memory (PM) deficits in ecstasy users (Hadjiefthyvoulou et al., 2011a, 2011b; Heffernan et al., 2001a, 2001b; Montgomery & Fisk, 2007; Rendell et al., 2007; Rendell et al., 2009; Zakzanis et al., 2003; see Chapter 6, Section 6.2 for further detail in relation to these studies). However, much of this research has focused on traditional indices of ecstasy use such as total lifetime exposure, duration of use, or current frequency of use. The present studies (Study 1 and Study 2) investigate the effects of short- and long-term ecstasy dose per session on PM performance. Ecstasy dose is a particularly important topic of investigation in the context of memory and learning in general since the absence of any dose-related effects might indicate that observed deficits are not attributable to ecstasy use. Rather, studies that report ecstasy-group-related impairments in PM but show no evidence of dose-related effects may merely reflect some premorbid condition or lifestyle factors unrelated to drug use.

Previous studies that report ecstasy-group-related deficits in PM have a number of limitations. One key problem concerns the way in which dose-related effects are studied. A

number of self-report studies have used the Prospective Memory Questionnaire (PMQ: Hannon et al., 1995, see Chapter 5, Section 5.1) and found evidence of PM deficits in ecstasy users (Heffernan et al., 2001a; Heffernan, et al., 2001b; Parrott et al., 2006). Despite this, no clear dose-related effects of ecstasy use on PM were reported. For example, in Heffernan and colleagues' (2001a) three-part study, ecstasy users reported significantly more short- and long-term PM errors on the PMQ. Although, this effect remained significant after controlling for other drug use, the authors did not directly explore the extent to which these effects were related to ecstasy use in a dose-related manner. Other research that has used the PMQ has assessed lifetime drug use categorically. That is, ecstasy users have been characterised according to their lifetime use based on the number of occasions that they have used ecstasy (0, 1-9, 10-99, 100+ occasions). Studies that have adopted this method have found that lifetime use was related to long-term self-reported PM problems on the PMQ (Rodgers et al., 2001). It is important to note that estimations of total lifetime ecstasy use were based on the number of occasions of ecstasy use rather than the number of ecstasy tablets consumed. In addition, lifetime ecstasy use for each participant was set at a midpoint of the particular range that they selected. Calculating lifetime ecstasy use in this manner is problematic given that the data obtained will be imprecise. For example, participants who report to having used ecstasy 10 times will be allocated to the same categorical group as those participants who report having used ecstasy 99 times. Thus, there is a degree of inaccuracy in using this method due to the ordinal nature of the scale. Lack of precision is further highlighted in that using occasions of use as an indicator of ecstasy dose does not enable researchers to determine the number of ecstasy tablets that have been consumed. Clearly, there will be differences in the typical dose of ecstasy consumed per session between different ecstasy users. Studies which have estimated dose according to the typical number of ecstasy tablets previously consumed have found no association between typical number of ecstasy tablets used and outcomes on the PMQ (e.g., Bedi & Redman, 2008a; Montgomery & Fisk, 2007).

Drawing on laboratory-based measures of PM, Zakzanis et al. (2003) used the Rivermead Behavioural Memory Test (RBMT) and found that currently abstinent ecstasy users made significantly more errors than nonusers on event- and time-based subscales of this measure. Scores on the 'appointment' subscales were significantly associated with the number of occasions of ecstasy use as well as the frequency of ecstasy use. In another study which used the RBMT and a modified version of the 2-minute associative cue task used by Hannon, Adonis, Harrington, Fries-Dias & Gibson (1995; upon the completion of each page

in a self-report questionnaire, participants were instructed to draw a cross at the bottom of the page), Bedi and Redman (2008b) found that ecstasy/polydrug group differences were either absent or inconclusive. In addition, dose-related effects were not reported. Rendell et al. (2007) used the Virtual Week task (Rendell & Craik, 2000, see Chapter 5, Section 5.3) and found that frequent ecstasy users (who used ecstasy more than once a fortnight) performed worse than infrequent users (using less than one a month) who in turn performed worse than non-ecstasy users on all PM subscales of this measure. More recently, Hadjiefthyvoulou et al. (2011a) used an extensive battery of laboratory-based PM measures and found that lifetime ecstasy use (estimated number of tablets) was significantly associated with event- and time-based PM scores on the CAMPROMPT. In another study from the same laboratory, lifetime ecstasy use was significantly associated with poor performance on the RBMT, the F1 event-based PM task and the delayed recall PM task (Hadjiefthyvoulou et al., 2011b). However, these effects were no longer significant following controls for other drug use indicating that the PM impairments observed were not attributable to lifetime ecstasy use.

In cases where dose-related effects are reported, they are often based on distinctions between broadly defined groups. Some studies compare 'heavy' versus 'moderate' users or 'frequent' versus 'infrequent' users (e.g., Rendell et al., 2007). However the group criteria across different studies is variable and different cut off points are often adopted. In relation the literature surrounding ecstasy use and cognitive outcomes in general, Reneman et al. (2006) used a lifetime consumption cut off of 55 tablets to categorise "heavy" and "moderate" ecstasy use. In comparison, participants in Gouzoulis-Mayfrank et al's (2003) study were considered to be "heavy" users if they had consumed more than 80 tablets and as "light" users if they had consumed less than 80 tablets in their lifetime. Other studies have set the cut off points at much higher levels of consumption. For example, Fisk and Montgomery (2009) set the dividing point at 1000 tablets. The use of varying cut off points in the literature makes it very difficult for researchers to reach definite conclusions when comparing the findings across studies.

Other studies have focused on the typical dose of ecstasy per session. Morefield, Keane, Felgate, White, and Irvine's (2011) natural observation explored the pharmacology of ecstasy use and focused on the relationship between the dose of ecstasy and MDMA plasma concentrations. Blood samples were taken from 56 'experienced' ecstasy users prior to the use of ecstasy. Further blood samples were taken one hour after use and for each hour thereafter during a five-hour test period. Blood samples were used to determine the amount of

ecstasy in plasma. Findings showed large differences in the drug use patterns (typical number of ecstasy tablets consumed per session) between ecstasy users. The typical number of tablets consumed per session ranged from 0.5 tablets to five or more tablets. Larger doses of ecstasy were associated with a non-linear accumulation of MDMA in plasma. In individuals who consumed only one ecstasy tablet or less, MDMA plasma concentrations were shown to peak after a few hours after use. In comparison, an escalating pattern of MDMA plasma concentration change was found in those individuals who consumed a larger number of tablets. This change did not reach a plateau during the five hours of the study period. A positive association was found between the number of tablets consumed in the session and the hour at which the highest MDMA plasma concentration was recorded. These findings clearly demonstrate the importance of ecstasy dose per session. For example, the consumption of one ecstasy tablet often or several ecstasy tablets per session infrequently may give rise to similar rates of lifetime consumption. However, variations in ecstasy dose per session can have very different consequences on MDMA plasma concentrations. Increased MDMA plasma concentrations which result from the use of multiple ecstasy tablets per session is likely to lead to increased exposure of MDMA within the brain compared to what would be found in from smaller doses. As a result, Morefield and co-workers argue that emphasis should be placed on the size of the typical dose rather than other measures such as frequency of use and total lifetime dose.

Evidence from neuroimaging studies further highlights the importance of the average dose of ecstasy per session. Thomasius et al. (2003) examined psychopathology, memory impairment and serotonergic alterations in 30 current ecstasy users, 31 ex-ecstasy users, 29 polydrug users and 30 drug naïve controls. The three drug user groups all showed increased psychopathology relative to the drug naïve control group. Reduced distribution volume ratios (DVRs) of serotonin transporter sites were found in subcortical regions (mesencephalon & caudate nucleus) of current ecstasy users. Typical dose of ecstasy per session was the best predictor of psychopathology and serotonergic alterations. Similar findings were reported by Kish et al. (2010) who found that SERT (serotonin transporter) binding was significantly reduced in a number of brain regions including the frontal, temporal, parietal, occipital, cingulate and insular cortices as well as in the hippocampus in ecstasy users. These abnormalities were significantly associated with the number of years of ecstasy use and the reported maximum single dose of ecstasy.

The research evaluated above highlights the importance of using a method of calculating ecstasy dose that captures subtle differences between drug users. The studies reported in this Chapter (Study 1 and Study 2) used a timeline technique similar to that adopted by Medina, Shear and Corcoran (2005) and Bedi and Redman (2008b) to further investigate ecstasy dose-related effects on PM performance. For each year that an individual has used ecstasy, they are asked to provide an estimate of typical dose per session and the frequency of use (number of times per week, month, etc). In addition, individuals are asked to provide estimates of typical dose per session and frequency of use for each month during the 12 months prior to the test-session. These data can then be used to calculate long and short-term average dose of ecstasy per session. The aforementioned measures of dose have received little attention previously especially in relation to PM. A control group of non-ecstasy users were included in the analyses. Groups were compared on a range of demographical and background variables including age, intelligence, years of education, daytime sleepiness (Epworth Sleepiness Scale), gender, cigarette and alcohol consumption, arousal, anxiety and depression. Groups were also compared on several long- and short-term indices of drug use. A range of laboratory-based PM tasks were administered throughout the test-session including the F1 event-based PM task (Hadjiefthyvoulou et al., 2011a), the long-term delayed recall PM task (Hadjiefthyvoulou et al., 2011a) and the Karolinska fatigue PM task (Hadjiefthyvoulou et al., 2011a; see Chapter 5, Section 5.3 for a detailed description of these PM tasks). Study 1 investigates the extent to which long-term average dose of ecstasy per session (average typical dose of ecstasy per session averaged over the entire period of use) can predict PM performance. Study 2 explores the extent to which short-term average dose of ecstasy per session (average typical dose of ecstasy per session over the previous 12 months) is associated with PM deficits.

Study 1

7.2 Method

Participants

Twenty-three long-term high dose (LTHD) ecstasy users (14 males), 19 long-term low dose (LTLD) ecstasy users (10 males) and 50 non-ecstasy users (22 males) took part in the investigation (for demographic variables, see Table 7.1). The gender composition did not differ significantly between the groups, $\chi^2(2)=1.86$, $p=.40$. Participants were recruited via direct approach to university students. All participants were university students attending Liverpool John Moores University (LJMU) or the University of Central Lancashire (UCLAN). Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence for LTHD ecstasy users was 32.17 weeks, median=8.00 weeks; the mean period of abstinence for LTLD ecstasy users was 39.87 weeks, median=9.00 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing. The present study was approved by the ethics committees of The University of Central Lancashire and Liverpool John Moores University in accordance with the guidelines of The British Psychological Society.

Materials

Patterns of ecstasy and other drug use were obtained via a background drug use questionnaire (Montgomery et al., 2005, see Appendix 1 for a copy of this questionnaire). The questions gauged the use of ecstasy and other drugs, as well as current age, years of education, general health and other relevant lifestyle variables (arousal, anxiety and depression). For each year since they commenced drug use, participants estimated the typical dose that they ingested in a representative session. Participants also estimated their typical frequency of use (number of sessions per week) during each specific year. This was done for all illicit drugs that were regularly consumed during each specific year. These data were then used to estimate total lifetime use for each drug, average long-term dose (typical dose of drug consumed in a single session, averaged over the entire period that an individual used the drug) and average frequency of use (typical frequency of use for each year (number of sessions per week) averaged over the entire period that an individual used the drug). The current use of cigarettes and alcohol were also assessed.

The Raven's Progressive Matrices test (Raven, Raven & Court, 1998) was used as a measure of fluid intelligence. This is a multiple-choice measure that contains a total of 60 incomplete abstract patterns. Participants were required to complete each pattern by selecting the missing item from a number of multiple-choice options. There were 5 sets of abstract patterns in total (i.e., Sets A to E) each containing 12 items (e.g., A1 through to A12, B1 through to B12). Each pattern in each set becomes increasingly difficult thus requiring higher cognitive capacity to encode and analyse information. Participants were given a score of one for every correct missing item selected whereby higher scores are indicative of increased fluid intelligence.

Daytime sleepiness was measured via the Epworth Sleepiness Scale (Johns, 1991, see Appendix 2 for a copy of this questionnaire). Participants were required to use a 4-point Likert scale (0=would never doze, 1=slight chance of dozing, 2=moderate chance of dozing, 3=high chance of dozing) to estimate the probability of them falling asleep in eight, everyday situations (e.g., while watching TV, in a car, while stopped for a few minutes in traffic). Scores from the eight situations were added together to give a total score out of 24. Scores in the 0-9 range were considered to be normal while scores in the 10-24 range were indicative of possible sleeping problems such as sleep apnoea.

Three laboratory measures of PM were administered including the F1 event-based PM task (Hadjiefthyvoulou et al., 2011a), the Long Term Recall PM task (Hadjiefthyvouolou et al., 2011a) and the fatigue PM task (Hadjiefthyvoulou et al., 2011a). A computer using MS-DOS was used for the F1 event-based PM task. Full descriptions of all laboratory measures of PM can be found in Chapter 5.

Procedure

Participants were informed of the general purpose of the experiment and verbal informed consent was obtained. Background questionnaires assessing age, years of education, general health and other relevant lifestyle variables (arousal, anxiety and depression, Daytime sleepiness) were administered first and in a counterbalanced order. The Raven's Progressive Matrices task, the F1 event-based PM task and the long-term delayed recall PM task were then administered in a counterbalanced order. The Karolinska fatigue PM task was administered throughout the test-session. Finally, a background drug use questionnaire was administered.

All tests were administered under laboratory conditions. Participants were fully debriefed and given the opportunity to ask any questions about the study prior to leaving the laboratory. Participants were paid £20 in store vouchers for their participation.

Design/Statistics

A median split was used to dichotomise long-term average dose of ecstasy per session (for each year the typical dose of ecstasy consumed in a single session was recorded and the resulting figures were averaged over the entire period that an individual had used the drug producing an annual average) and thus create two user groups (LTHD ecstasy users and LTLD ecstasy users). The median for long-term average dose of ecstasy per session was 2.00 tablets. Participants who, on average, consumed 2.00 or more ecstasy tablets per session throughout their period of use were classified as LTHD ecstasy users. Participants who, on average, consumed less than 2.00 ecstasy tablets per session were classified as LTLD ecstasy users.

All measures were analysed using a between-participant design with user group as the independent variable (LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users). Age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale Score, arousal, anxiety and depression were included as background measures. Any group differences on these background variables were investigated using one-way ANOVA. Total ecstasy, cannabis and cocaine consumption, long-term average dose of ecstasy, cannabis and cocaine use, duration of ecstasy, cannabis and cocaine use, long-term (average weekly consumption averaged over lifetime for ecstasy, cannabis and cocaine) frequency of ecstasy, cannabis and cocaine use and the number of weeks since ecstasy, cannabis and cocaine were last used were included as background drug use variables.

Data for total lifetime ecstasy, cannabis and cocaine use, long-term average dose of ecstasy, cannabis and cocaine per session, the duration of ecstasy, cannabis and cocaine use, the long-term average frequency of ecstasy, cannabis and cocaine use and the current frequency of ecstasy, cannabis and cocaine use were not normally distributed. This was characterised by skew or kurtosis associated with z values exceeding 3.29, $p<.001$. As a result non-parametric analyses were used (Tabachnick & Fidell, 2001).

7.3 Results

Demographical and Background Variables

The scores for the demographical variables and background variables of age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression are set out in Table 7.1. LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users were compared on a number of background drug use variables (total lifetime drug use, long-term average dose per session, total duration of drug use in weeks, long-term frequency of drug use and the number of weeks since drugs were last used) and these data are shown in Table 7.2.

Table 7.1 Demographical variables of long-term high dose ecstasy users, long-term low dose ecstasy users and non-ecstasy users.

	LTHD ecstasy users		LTLD ecstasy users		Non-ecstasy users		p
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
Age (years)	21.91 (2.11)	23	23.53 (7.20)	19	20.92 (2.22)	50	<.001***
Raven's Progressive Matrices (max 60)	47.00 (5.84)	23	47.76 (7.20)	17	48.25 (6.40)	48	.75
Years of education	16.22 (1.78)	23	17.45 (1.99)	20	16.15 (2.00)	48	.04*
Alcohol (units per week)	14.43 (8.73)	22	13.08 (10.15)	19	11.68 (8.68)	45	.50
Cigarettes per day	6.68 (3.51)	14	5.40 (4.47)	11	4.80 (3.29)	5	.57
Epworth Sleepiness Score	6.68 (2.71)	22	7.45 (3.61)	20	5.95 (3.66)	49	.25
Arousal	19.59 (4.54)	22	18.63 (3.88)	19	19.85 (4.51)	46	.60
Anxiety	11.55 (2.40)	22	11.89 (3.10)	18	11.70 (4.10)	46	.96
Depression	12.14 (3.31)	22	13.11 (3.41)	19	12.87 (3.56)	46	.61

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

One-way ANOVA revealed a significant difference between the groups in terms of age. Tukey's post hoc test showed that non-ecstasy users were significantly younger than LTLD ecstasy users. There was no significant difference in age between non-ecstasy users and LTHD ecstasy users. The age difference between LTHD ecstasy users and LTLD ecstasy users did approach statistical significance, such that LTHD ecstasy users were younger than LTLD ecstasy users (see Appendix 3 for detailed statistical analyses in relation to background variables).

LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users differed significantly from each other in terms of number of years of education. Tukey's post hoc test showed that non-ecstasy users had studied for a significantly shorter period of time compared to LTLD ecstasy users. The difference in years of education between LTHD ecstasy users and LTLD ecstasy users approached statistical significance. The number of years of education completed by non-ecstasy users and LTHD ecstasy users did not differ significantly from each other. A series of one-way ANOVAs revealed that the groups did not differ significantly in terms of intelligence, cigarette and alcohol consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression (see Appendix 3 for detailed statistical analyses related to background variables).

Table 7.2 Background drug use variables of long-term high dose ecstasy users, long-term low-dose ecstasy users and non-ecstasy users.

	LTHD ecstasy users					LTLD ecstasy users					Non-ecstasy users					p
	Med.	Min.	Max.	Int. Range	n	Med.	Min.	Max.	Int. Range	n	Med.	Min.	Max.	Int. Range	n	
Total prior consumption																
Ecstasy (tablets)	367.00	2.00	12921.00	957.00	23	20.00	1.00	492.50	42.11	19	-	-	-	-	-	.01**
Cannabis (joints)	313.00	.00	11376.00	993.50	19	631.13	.00	9158.00	2797.00	18	20.00	.00	1092.00	16.00	21	<.001***
Cocaine (lines)	290.50	.00	5684.00	1063.00	18	120.25	.00	4816.00	452.00	12	3.50	.00	81.00	.00	5	.39
Long-term average dose per session																
Ecstasy	2.67	2.00	12.25	2.00	23	1.00	.29	1.78	.51	20	-	-	-	-	-	<.001***
Cannabis	2.36	.50	5.80	3.17	18	1.83	.75	8.75	2.00	18	1.00	.07	4.00	1.36	18	.04*
Cocaine	6.00	1.00	46.40	7.30	19	2.25	.13	10.00	4.50	12	2.00	1.00	4.50	-	3	.04*
Duration of use (number of weeks)																
Ecstasy	148.00	52.00	519.43	209.29	23	135.00	.00	772.00	357.75	19	-	-	-	-	-	.03*
Cannabis	259.00	.00	544.00	250.00	18	325.93	68.00	831.00	252.54	18	129.00	.00	540.00	251.25	22	.002**
Cocaine	136.29	.00	430.00	210.22	18	216.00	.00	488.00	309.50	12	17.58	.00	48.00	44.79	4	.60
Long-term frequency of use (number of occasions of use per week)																
Ecstasy	.49	.00	1.00	.90	23	.08	.01	1.50	.29	20	-	-	-	-	-	<.001***
Cannabis	.92	.02	4.00	1.77	18	.37	.02	4.56	1.92	18	.20	.00	2.50	.34	18	.04*
Cocaine	.23	.02	1.32	1.44	19	.21	.02	.40	.68	12	.08	.05	.75	-	3	.98
Number of weeks since last use																
Ecstasy	14.00	.57	260.00	81.00	23	12.00	.57	208.00	207.43	20	-	-	-	-	-	.73
Cannabis	16.00	.00	312.00	51.22	20	2.00	.14	156.00	23.86	19	14.00	.26	260.00	114.50	22	.11
Cocaine	3.50	.43	208.00	25.97	20	10.00	2.00	260.00	25.00	12	20.00	.85	124.00	71.58	5	.14

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

With regard to total lifetime drug use, the medians show that LTHD ecstasy users consumed more ecstasy tablets over their lifetime compared to LTLD ecstasy users. Mann-Whitney U test showed that LTHD ecstasy users consumed significantly more ecstasy tablets over their lifetime compared to LTLD ecstasy users, U=128.00, p=.01. The medians indicate that LTLD ecstasy users consumed more cannabis over their lifetime relative to LTHD ecstasy users and non-ecstasy users. LTHD ecstasy users consumed more cannabis over their lifetime relative to non-ecstasy users. Kruskal-Wallis tests revealed that there was a significant difference between the groups in terms of total lifetime consumption of cannabis, $\chi^2(2)=14.34$, $p<.001$, Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) showed that LTLD ecstasy users had consumed significantly more cannabis over their lifetime compared to non-ecstasy users, U=64.50, $p<.001$.

Unsurprisingly, the median data shows that the long-term average dose of ecstasy per session was higher for LTHD ecstasy users compared to LTLD ecstasy users with LTHD ecstasy users typically consuming more ecstasy tablets per session than LTLD ecstasy users, U=.00, $p<.001$. Averaged across lifetime use, LTLD ecstasy users consumed higher doses of cannabis per session compared to LTHD ecstasy users and non-ecstasy users. The long-term average dose of cannabis use per session was higher for LTHD ecstasy users compared to non-ecstasy users. There was a significant difference between the groups in long-term average dose of cannabis per session, $\chi^2(2)=6.29$, p=.04. The median data indicates that the long-term average dose of cocaine per session was higher for LTHD ecstasy users compared to LTLD ecstasy users. LTHD ecstasy users consumed significantly more cocaine per session compared to LTLD ecstasy users, U=64.50, p=.04.

In terms of duration of drug use, the median data shows that LTLD ecstasy users had been using ecstasy for longer than LTHD ecstasy users with Mann-Whitney U test showing that this difference was statistically significant, U=151.00, p=.03. The median data indicates that the duration of cannabis use was higher for LTLD ecstasy users compared to LTHD ecstasy users and non-ecstasy users. LTHD ecstasy users had been using cannabis for longer than non-ecstasy users. There was a significant difference between the groups in terms the duration of cannabis use, $\chi^2(2)=12.18$, p=.002 such that LTLD ecstasy users had used cannabis for a significantly longer duration of time compared to non-ecstasy users, U=75.00, p=.001.

In terms of long-term frequency of drug use, LTHD ecstasy users used ecstasy more frequently during their lifetime compared to LTLD ecstasy users, U=10.50, $p<.001$. The median data shows that LTHD ecstasy users used cannabis more frequently over their lifetime than LTLD ecstasy users and non-ecstasy users. LTLD ecstasy users used cannabis more frequently over their lifetime compared to non-ecstasy users. There was a significant difference between LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users in terms their long-term frequency of cannabis use, $\chi^2(2)=6.28$, $p=.04$.

For all outcomes of cocaine use, comparisons were restricted to the two ecstasy user groups given that there was only a small number of non-ecstasy users who had consumed cocaine (between three and five participants). Non-significant inferential statistics for outcomes in Table 7.2 are reported in Appendix 3.

Laboratory-based measures

Outcomes for the laboratory-based measures of PM for long-term high dose ecstasy users, LTLD ecstasy users and non-ecstasy users are summarised in Table 7.3 and 7.4.

Table 7.3 Means and Standard Deviations (SD) for long-term high dose ecstasy users, long-term low dose ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall task and the Karolinska fatigue PM task.

	LTHD ecstasy users n=23	LTLD ecstasy users n=20	Non-ecstasy users n=50
	Mean (SD)	Mean (SD)	Mean (SD)
F1 event-based PM task			
Trial 1 Errors	.74 (1.25)	.55 (1.10)	.52 (1.01)
Trial 2 Errors	.13 (.63)	.30 (.80)	.12 (.48)
Trial 3 Errors	.22 (.67)	.10 (.31)	.06 (.42)
Total Errors	1.09 (2.07)	.95 (1.47)	.70 (1.54)
Long-term delayed recall PM task			
Total number of recall tests returned (max of 3)	1.30 (1.43)	.90 (1.25)	1.35 (1.36)
Karolinska fatigue PM task			
Percentage completed in first half of test-session	86.23 (23.52)	91.33 (12.37)	88.61 (21.05)
Percentage completed in second half of test-session	54.56 (32.88)	54.17 (25.37)	70.63 (28.97)
Percentage completed overall	70.03 (22.66)	71.82 (14.68)	79.38 (19.14)

Table 7.4 Median (Med.), Minimum (Min.), Maximum (Max.) and Interquartile Range (Int. Range) scores for long-term high dose ecstasy users and long-term low dose ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall task and the Karolinska fatigue PM task.

	LTHD ecstasy users n=23				LTLD ecstasy Users n=20				Non-ecstasy users n=50				p
	Median	Min.	Max.	Int. Range	Median	Min.	Max.	Int. Range	Median	Min.	Max.	Int. Range	
F1 event-based PM task													
Trial 1 Errors	.00	.00	3.00	1.00	.00	.00	3.00	.75	.00	.00	3.00	1.00	.85
Trial 2 Errors	.00	.00	3.00	.00	.00	.00	3.00	.00	.00	.00	3.00	.00	.46
Trial 3 Errors	.00	.00	3.00	.00	.00	.00	3.00	.00	.00	.00	3.00	.00	.17
Total Errors	.00	.00	9.00	1.00	.00	.00	5.00	1.75	.00	.00	9.00	1.00	.57
Long-term delayed recall PM task													
Total number of recall tests returned (max of 3)	1.00	.00	3.00	3.00	.00	.00	3.00	2.00	1.00	.00	3.00	3.00	.40
Karolinska fatigue PM task													
Percentage completed in first half of test-session	100.00	25.00	100.00	33.33	100.00	66.67	100.00	23.75	100.00	10.00	100.00	25.00	.94
Percentage completed in second half of test-session	50.00	.00	100.00	55.00	50.00	.00	100.00	50.00	70.84	.00	100.00	50.00	.04*
Percentage completed overall	75.00	22.22	100.00	33.33	75.00	33.00	100.00	13.54	83.33	38.00	100.00	34.00	.11

*p<.05, *Note.* n for non-ecstasy users was variable such that there were only 49 non-ecstasy users who completed the long-term delayed recall PM task and 48 non-ecstasy users who completed the Karolinska fatigue PM task.

The distributions of the data for Trial 1 errors (Skew, z=6.68 and Kurtosis, z=2.25), Trial 2 errors (Skew, z=16.40 and Kurtosis, z=35.88), Trial 3 errors (Skew, z=20.08 and Kurtosis, z =54.96) and total errors (Skew, z=12.16 and Kurtosis, z=23.49) on the F1 event-based, for the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed in the first half of the test-session only, Skew, z=-7.36 and Kurtosis, z=6.20) and for the long-term delayed recall PM task (Skew, z=1.40 and Kurtosis, z=-3.51) deviated significantly from normality. This was characterised by the skew and/or kurtosis z scores exceeding 3.29, $p<.001$ (Tabachnick & Fidell, 2001). Group differences were investigated via Kruskal-Wallis test with follow-up post hoc Mann-Whitney U tests (with full Bonferroni correction, adjusted alpha level=.017).

Where the distributions were normal, one-way ANOVAs were used to investigate group differences on two aspects of the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and overall). ANOVAs were followed up with Helmert contrasts and pairwise comparisons.

Examination of the data in Table 7.4 reveals that LTHD ecstasy users made more errors than LTLD ecstasy users and non-ecstasy users on Trial 1 and Trial 3 of the F1 event-based PM task. LTLD ecstasy users and non-ecstasy users made a similar number of errors on these trials. In addition, LTLD ecstasy users made more errors than LTHD ecstasy users and non-ecstasy users on Trial 2 while LTHD ecstasy users and non-ecstasy users made a similar number of errors on this trial. LTHD ecstasy users and LTLD ecstasy users made more errors overall (combined error rate across all three trials) relative to non-ecstasy users. Data for Trial 1 errors, Trial 2 errors, Trial 3 errors and total errors on the F1 event-based PM task were all significantly non-normal. Kruskal-Wallis tests revealed that there was no significant difference between the groups in terms of errors made on Trial 1, $\chi^2(2)=.34$, $p=.85$, Trial 2, $\chi^2(2)=1.57$, $p=.46$, or Trial 3 , $\chi^2(2)=3.56$, $p=.17$ of the F1 event-based PM task. In addition, the groups did not differ in terms of total number of errors made across all trials on the F1 event-based PM task, $\chi^2(2)=1.14$, $p=.57$.

With regard to long-term time-based PM performance, inspection of the data in Table 7.4 reveals that LTHD ecstasy users and non-ecstasy users remembered to return more delayed recall tests compared to LTLD ecstasy users. LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users did not differ significantly on the long-term delayed recall PM task, $\chi^2(2)=1.84$, $p=.40$.

In relation to short-term time-based PM performance, inspection of the data in Table 7.4 reveals that relative to LTHD ecstasy users and non-ecstasy users, LTLD ecstasy users remembered to complete a greater proportion of Karolinska fatigue questionnaires during the first half of the test-session.. There was no significant difference between LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users in terms of the proportion of Karolinska fatigue questionnaires completed in the first half of the test-session, $\chi^2(2)=.12$, $p=.94$.

Non-ecstasy users completed a greater proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to LTHD ecstasy users and LTLD ecstasy users. LTHD ecstasy users and LTLD ecstasy users remembered to complete a similar proportion of Karolinska fatigue questionnaires during the second half of the test-session. One-way ANOVA revealed that there was a significant difference between the groups in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session, $F(2,88)=3.49$, $p=.04$, partial eta squared=.07). Helmert contrasts revealed that the combined user group of LTHD ecstasy users and LTLD ecstasy users completed a significantly lower proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to non-ecstasy users, $p=.01$. However, further Helmert contrast revealed that LTHD ecstasy users and LTLD ecstasy did not differ significantly, $p=.97$. Pairwise comparisons adjusted by Bonferroni correction (three pairwise comparison and as such the significant alpha level was set at .017) revealed that the difference in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session between LTHD ecstasy users (M=54.56, SD=32.88) and non-ecstasy users (M=70.63, SD=28.97) ($p=.03$), LTLD ecstasy users (M=54.17, SD=25.37) and non-ecstasy users, $p=.04$ was just short of significance. LTHD ecstasy users and LTLD ecstasy users did not differ significantly, $p=.97$.

Inspection of the data in Table 7.4 reveals that over the entire test-session, non-ecstasy users completed a greater proportion of Karolinska fatigue questionnaires than LTHD ecstasy users and LTLD ecstasy users. One-way ANOVA revealed that there was no significant difference between the three groups in terms of the proportion of Karolinska fatigue questionnaires completed during the entire test-session, $F(2,88)=2.27$, $p=.11$, partial eta squared =.05. However, Helmert contrasts revealed that there was a significant difference in the proportion of Karolinska fatigue questionnaires completed during the entire test-session between the combined user group of LTHD ecstasy users and LTLD ecstasy users and non-ecstasy users, $p=.04$. Further Helmert contrasts showed that there was no significant difference in the

proportion of Karolinska fatigue questionnaires during the entire test-session between LTHD ecstasy users and LTLD ecstasy users, *p*=.76. Pairwise comparisons adjusted for Bonferroni correction (three pairwise comparisons and as such the significant alpha level was set at .017) revealed that there was no significant difference in the proportion of Karolinska fatigue questionnaires completed during the entire test-session between LTHD ecstasy users (M=70.03, SD=22.66) and non-ecstasy users (M=79.38, SD=19.14),*p*=.06, LTLD ecstasy users (M=71.82, SD=14.68) and non-ecstasy users. *p*=.14, or LTHD ecstasy users and LTLD ecstasy users, *p*=.76.

Study 2

7.4 Method

Participants

The participants in the present study were the same as those who participated in Study 1.[1] They were divided into 21 short-term high dose (STHD) ecstasy users (11 males, 10 females), 23 short-term low dose (STLD) ecstasy users (10 males, 13 females) and 50 non-ecstasy users (22 males, 28 females). The gender composition did not differ significantly between the groups, $\chi^2(2)=1.12$, $p=.57$. The mean period of abstinence for STHD ecstasy users was 4.70 weeks, median=3 weeks; the mean period of abstinence for STLD ecstasy users was 78.83 weeks, median=52.00 weeks).

Materials

Materials are as per Study 1. Additionally, from the background drug use questionnaire, for the 12 month period prior to the test-session, participants estimated the typical dose that they ingested in a representative session for each month. Participants also estimated their typical frequency (times per week) in the 12 month period prior to the test-session. This was done for all illicit drugs during the 12 months prior to the test-session. Long-term data relating to drug use was collected as in Study 1. Estimates of total use for each respective drug and their average frequency of use (times per week) during the previous 12 months were calculated.

Procedure

Procedural details were reported in Study 1.

Design/Statistics

A median split was used to dichotomise short-term average dose of ecstasy per session (the typical dose of ecstasy consumed in a single session during each of the 12 months prior to the test-session; months during which the drug was not used are coded as zero) and thus create two user groups (STHD ecstasy users and STLD ecstasy users). The median split for short-term average dose of ecstasy per session was .17 tablets per session. Participants who, on average, consumed .17 or more ecstasy tablets per session during the 12 months prior to the test-session were classified as STHD ecstasy users. Participants who, on average, consumed

[1] The total number of ecstasy users in Study 2 exceeded those in Study 1 as a result of missing data.

less than .17 ecstasy tablets per session during the 12 months prior to the test-session were classified as LTLD ecstasy users. The fact that the median was less than 1 indicates that a majority of users experienced a number of months when they were in fact abstinent. This applied to all members of the light user group and to a proportion of the heavy user group. The high and low dose groups together with a non-ecstasy user group constituted the three levels of the between participant IV.

The background measures and indeed the underlying data were the same as were used in Study 1 as were the PM DVs. However, the group classifications were based on short-term ecstasy use as indicated above. Alternative background drug use variables were used. These included total ecstasy, cannabis and cocaine consumption in the previous 12 months, average typical ecstasy, cannabis and cocaine dose per session in the previous 12 months, average frequency (times per week) of ecstasy, cannabis and cocaine use in the previous 12 months and total ecstasy, cannabis and cocaine consumption in the previous 30 days. In light of the distributional characteristics of the individual measures, and the tripartite nature of the IV, the same mix of parametric and non-parametric analyses were employed as in Study 1.

7.5 Results

Demographical and Background Variables

Demographic and background scores (age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression) are set out in Table 7.5 Various indices of short-term background drug use including total ecstasy, cannabis and cocaine consumption, average typical ecstasy, cannabis and cocaine dose per session and average frequency of ecstasy, cannabis and cocaine use (times per week) in the previous 12 months were compared between STHD ecstasy uses, STLD ecstasy users and non-ecstasy users. Total ecstasy, cannabis and cocaine use in the 30 days prior to the test-session were also compared between the groups. These data are shown in Table 7.6.

Table 7.5 Demographical variables of short-term high dose ecstasy users, short-term low dose ecstasy users and non-ecstasy users.

	STHD ecstasy users		STLD ecstasy users		Non-ecstasy users		p
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
Age (years)	22.48 (2.94)	21	22.52 (2.27)	23	20.92 (2.22)	50	.01**
Raven's Progressive Matrices (max 60)	45.90 (6.44)	20	47.95(6.42)	22	48.25 (6.40)	48	.38
Years of education	16.68 (2.32)	22	16.74 (1.57)	23	16.15 (2.00)	45	.39
Alcohol (units per week)	15.05 (9.25)	22	12.14 (9.00)	21	11.68 (8.68)	45	.34
Cigarettes per day	6.33 (3.72)	15	6.17 (4.37)	11	4.80 (3.29)	50	.74
Epworth Sleepiness Score	6.28 (2.72)	21	8.00 (3.54)	23	5.96 (3.66)	49	.39
Arousal	17.90 (4.44)	20	19.91 (3.82)	23	19.85 (4.51)	46	.21
Anxiety	11.63 (2.48)	19	11.74 (2.86)	23	11.70 (4.10)	46	1.00
Depression	12.85 (3.65)	20	12.57 (3.09)	23	12.87 (3.36)	46	.94

**$p<.01$

One-way ANOVA showed that there was a significant difference between the groups in terms of age. Tukey's post hoc test showed that non-ecstasy users were significantly younger than STHD ecstasy users and STLD ecstasy users. There was no significant difference in age between STHD ecstasy users and STLD ecstasy users. A series of one-way ANOVAs revealed no significant differences between the groups in terms of intelligence (Raven's Progressive Matrices), years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale Score, arousal, anxiety, and depression (see Appendix 3 for detailed statistical analyses related to background variables for STHD ecstasy users, STLD ecstasy users and non-ecstasy users).

Table 7.6 Background drug use variables of short-term high dose ecstasy users, short-term low dose ecstasy users and non-ecstasy users.

	STHD ecstasy users					STLD ecstasy users					Non-ecstasy users					p
	Median	Min.	Max.	Int. Range	n	Median	Min.	Max.	Int. Range	n	Median	Min.	Max.	Int. Range	n	
Total use in the last 12 months																
Ecstasy (tablets)	33.52	3.00	379.00	105.40	22	.00	.00	3.00	1.00	23	-	-	-	-	-	<.001***
Cannabis (joints)	48.00	.00	2079.00	671.75	21	2.00	.00	1344.00	44.25	20	.08	.00	144.00	2.50	23	.01**
Cocaine (lines)	17.25	.00	768.00	114.00	20	8.00	.00	424.00	26.00	15	3.50	.00	81.00	48.50	5	.50
Average typical dose of drug over the previous 12 months																
Ecstasy	1.08	.25	4.17	1.73	22	.00	.00	.17	.08	23	-	-	-	-	-	<.001***
Cannabis	1.50	.00	8.00	3.79	21	.24	.00	4.33	1.35	20	.08	.00	3.00	.21	23	.02*
Cocaine	1.04	.00	14.67	5.56	20	.67	.00	8.83	1.38	15	.25	.00	2.25	1.23	5	.42
Average frequency of use in the last 12 months (times per week)																
Ecstasy	.41	.06	2.50	.67	22	.00	.00	.13	.02	23	-	-	-	-	-	<.001***
Cannabis	.63	.00	7.00	3.74	21	.03	.00	7.00	.43	20	.00	.00	1.00	.10	23	.01*
Cocaine	.08	.00	3.43	.56	20	.02	.00	1.00	.29	15	.02	.00	.38	.35	5	.44
Total use in the last 30 days																
Ecstasy (tablets)	1.24	.00	20.00	4.50	22	.00	.00	.00	.00	20	-	-	-	-	-	<.001***
Cannabis (joints)	3.00	.00	240.00	53.88	21	.00	.00	120.00	.75	18	.00	.00	12.00	4.29	21	<.001***
Cocaine (lines)	.50	.00	96.00	9.00	18	.00	.00	64.00	4.00	14	.00	.00	1.00	.50	5	.32
Number of weeks since last use																
Ecstasy	3.50	.57	12.00	7.04	22	52.00	8.00	260.00	128.00	23	-	-	-	-	-	<.001***
Cannabis	1.00	.00	312.00	39.86	21	18.00	.14	156.00	32.25	20	14.00	.26	260.00	114.50	22	.03*
Cocaine	20.00	.85	124.00	71.59	19	24.00	.43	260.00	153.00	15	4.00	.43	28.00	10.00	5	.04*

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

With regard to total drug use in the 12 months prior to the test-session, the relevant medians show that STHD ecstasy users consumed more ecstasy in the previous 12 months compared to STLD ecstasy users. Mann-Whitney U test revealed that this difference was statistically significant, U=.50, p<.001. The median data indicates that STHD ecstasy users consumed more cannabis in the previous 12 months compared to both STLD ecstasy users and non-ecstasy users. STLD ecstasy users consumed more cannabis in the previous 12 months relative to non-ecstasy users. Kruskal-Wallis test showed that the groups differed significantly in terms of total cannabis consumption in the previous 12 months, $\chi^2(2)=8.71$, p=.01. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) revealed that STHD cannabis users consumed significantly more cannabis in the previous 12 months compared to non-ecstasy users, U=125.50, p=.005. The difference between short-term high dose ecstasy users and short-term low dose ecstasy users was not significant, U=139.50, p=.06.

In accordance with the manner in which the groups were defined, in relation to short-term average dose, the median data indicates that on average, STHD ecstasy users typically consumed more ecstasy tablets per session in the previous 12 months compared to STLD ecstasy users with Mann-Whitney U test revealing that the difference was statistically significant, U=.00, p<.001. The median data shows that the average typical dose of cannabis per session in the previous 12 months was higher for STHD ecstasy users compared to STLD ecstasy users and non-ecstasy users. The average dose of cannabis per session in the previous 12 months was higher for STLD ecstasy users relative to non-ecstasy users. There was a significant difference between the groups in terms of the typical average dose of cannabis per session in the previous 12 months, $\chi^2(2)=8.29$, p=.02. STHD ecstasy users consumed higher typical average doses of cannabis per session in the previous 12 months compared to non-ecstasy users, U=131.00, p=.008.

In terms of the average short-term frequency (times per week) of drug use, the median data reveals that STHD ecstasy users consumed ecstasy more frequently during the previous 12 months compared to STLD ecstasy users. Mann-Whitney U test revealed that the difference was statistically significant, U=8.00, p<.001. The median data shows that STHD ecstasy users consumed cannabis more frequently in the previous 12 months compared to STLD ecstasy users and non-ecstasy users. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of average frequency of cannabis use in the previous 12 months, $\chi^2(2)=9.28$, p=.01.

With regard to recent drug use, the median data indicates that STHD ecstasy users had used more ecstasy in the 30 days prior to the test-session relative to STLD ecstasy users. STLD ecstasy users had not used any ecstasy in the 30 days prior to the test-session. Mann-Whitney U test revealed that this difference was statistically significant, U=90.00, $p<.001$. The median data shows that STHD ecstasy users had used more cannabis in the 30 days prior to test-session compared to STLD ecstasy users and non-ecstasy users. STLD ecstasy users had used more cannabis in the previous 30 days compared to non-ecstasy users. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of total cannabis consumption in the previous 30 days, $\chi^2(2)=16.73$, $p<.001$. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) revealed that STHD ecstasy users consumed significantly more cannabis in the previous 30 days than STLD ecstasy users, U=89.50, $p=.004$, and non-ecstasy users U=84.50, $p<.001$.

In relation to period of abstinence, the median data shows that STHD ecstasy users had used ecstasy more recently than STLD ecstasy users with Mann-Whitney U test revealing that the difference was statistically significant, U=6.00, $p<.001$. The median data indicates that STHD ecstasy users and STLD ecstasy users had used cannabis more recently than non-ecstasy users. The period of abstinence from cannabis use was similar for STHD ecstasy users and STLD ecstasy users. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of the number of weeks since they last used cannabis, $\chi^2(2)=7.05$, $p=.03$. Mann-Whitney U tests showed that STHD ecstasy users had a significantly shorter period of abstinence from cannabis use relative to non-ecstasy users, U=127.00, $p=.01$). The median data shows that STHD ecstasy users had used cocaine more recently than STLD ecstasy users with Mann-Whitney U test revealing that the difference was statistically significant, U=84.00, $p=.04$.

For all outcomes of short-term cocaine use, comparisons were restricted to the two concurrent alcohol and ecstasy user groups given that only two non-ecstasy users had consumed cocaine. Inferential statistics for those outcomes in Table 7.6 that were not significant are reported in Appendix 3.

Laboratory-based measures

Outcomes for the laboratory-based measures of PM for STHD ecstasy users, STLD ecstasy users and non-ecstasy users are summarised in Table 7.7 and Table 7.8.

Table 7.7 Mean and Standard Deviations (SD) for short-term high dose ecstasy users, short-term low dose ecstasy users and non-ecstasy users on the F1 event-based PM task, the Long-term Delayed Recall Task and the Karolinska fatigue PM task.

	STHD ecstasy users n=22	STLD ecstasy users n=23	Non-ecstasy users n=50
	Mean (SD)	Mean (SD)	Mean (SD)
F1 event-based PM task			
Trial 1 Errors	.67 (1.20)	.64 (1.18)	.52 (1.01)
Trial 2 Errors	.14 (.14)	.27 (.88)	.12 (.48)
Trial 3 Errors	.19 (.19)	.14 (.64)	.06 (.42)
Total Errors	1.00 (1.41)	1.05 (2.13)	.70 (1.54)
Long-term delayed recall PM task			
Total number of recall tests returned (max of 3)	1.24 (1.37)	1.00 (1.35)	1.35 (1.36)
Karolinska fatigue PM task			
Percentage completed in first half of test-session	87.35 (21.05)	89.71 (21.22)	88.61 (21.05)
Percentage completed in second half of test-session	39.85 (30.46)	66.81 (23.07)	70.62 (28.97)
Percentage completed overall	63.61 (19.23)	77.09 (17.76)	79.38 (19.14)

Note: n for all groups was variable as a result of missing data. There were only 21 STHD ecstasy users who completed the F1 event-based PM task and the long-term delayed recall PM task. Only 22 short-term low-dose ecstasy users completed the F1 event-based PM task. Forty-Nine non-ecstasy users completed the long-term delayed recall PM task and 48 non-ecstasy users completed the Karolinska fatigue PM task.

Table 7.8 Median, Minimum (Min.), Maximum (Max.) and Interquartile Range (Int. Range) scores for short-term high dose ecstasy users, short-term low dose ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall task and the Karolinska fatigue PM task.

	STHD ecstasy users n=22				STLD ecstasy users n=23				Non-ecstasy users n=50				p
	Median	Min.	Max.	Int. Range	Median	Min.	Max.	Int. Range	Median	Min.	Max.	Int. Range	
F1 event-based PM task													
Trial 1 Errors	.00	.00	3.00	1.00	.00	.00	3.00	1.00	.00	.00	3.00	1.00	.98
Trial 2 Errors	.00	.00	2.00	.00	.00	.00	3.00	.00	.00	.00	3.00	.00	.98
Trial 3 Errors	.00	.00	1.00	.00	.00	.00	3.00	.00	.00	.00	3.00	.00	.06
Total Errors	.00	.00	5.00	1.25	.00	.00	9.00	1.00	.00	.00	9.00	1.00	.48
Long-term delayed recall PM task													
Total number of recall tests returned (max of 3)	1.00	.00	3.00	3.00	.00	.00	3.00	3.00	1.00	.00	3.00	3.00	.68
Karolinska fatigue PM task													
Percentage completed in first half of test-session	100.0	50.00	100.00	27.08	100.00	25.00	100.00	75.00	100.00	10.00	100.00	25.00	.61
Percentage completed in second half of test-session	40.00	.00	100.00	37.50	75.00	20.00	100.00	30.00	70.84	.00	100.00	50.00	p<.001***
Percentage completed overall	64.59	22.22	100.00	25.00	77.79	33.33	100.00	18.89	83.33	38.00	100.00	33.83	.01**

**p<.01, ***p<.001 *Note:* n for all groups was variable as a result of missing data. There were only 21 STHD ecstasy users who completed the F1 event-based PM task and the long-term delayed recall PM task. Only 22 short-term low-dose ecstasy users completed the F1 event-based PM task. Forty-Nine non-ecstasy users completed the long-term delayed recall PM task and 48 non-ecstasy users completed the Karolinska fatigue PM task.

Inspection of the data in Table 7.8 reveals that non-ecstasy users made fewer errors than STHD ecstasy users and STLD ecstasy users on all Trials of The F1 event-based PM task. A series of Kruskal-Wallis tests showed that STHD ecstasy users, STLD ecstasy users and non-ecstasy users did not differ significantly from each other in terms of errors made on Trial 1, $\chi^2(2)=.05$, $p=.98$, and Trial 2, $\chi^2(2)=.04$, $p=.98$, of the F1 event-based PM task.

However, with regard to the errors made on Trial 3, the difference between the groups approached statistical significance, $\chi^2(2)=5.54$, $p=.06$. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) showed that STHD ecstasy users made significantly more errors than non-ecstasy users on Trial 3 of the F1 event-based PM task, U=463.00, $p=.016$ No significant differences were found between STLD ecstasy users and non-ecstasy users, U=231.00, $p=.40$ or STHD ecstasy users and STLD ecstasy users, U=537.00, $p=.19$ in terms of the errors made on Trial 3 of the event-based PM task. The three groups did not differ significantly from each other in terms of the total errors made across all three trials on The F1 event-based PM task, $\chi^2(2)=1.48$, $p=.48$.

In terms of long-term time-based PM performance, inspection of the data in Table 7.8 shows that STLD ecstasy users returned a fewer number of delayed recall tests (the long-term delayed recall test) compared to STHD ecstasy users and non-ecstasy users. STHD ecstasy users and non-ecstasy users returned a similar number of delayed recall tests. Kruskal-Wallis test showed that there was no significant difference in the number of delayed recall task completed by STHD ecstasy users, STLD ecstasy users and non-ecstasy users, $\chi^2(2)=.77$, $p=.68$.

With regard to short-term time-based PM, inspection of the data in Table 7.8 reveals that STHD ecstasy users, STLD ecstasy users and non-ecstasy users completed a similar number of Karolinska fatigue questionnaires during the first half of the test-session. Kruskal-Wallis test showed that there was no significant difference between the three groups in terms of the proportion of Karolinska questionnaires completed in the first half of the test-session, $\chi^2(2)^{=}99$, $p=.61$.

The data in Table 7.8 shows that non-ecstasy users successfully completed a higher proportion of Karolinska fatigue questionnaires during the second half of the test-session compared STHD ecstasy users and STLD ecstasy users. STLD ecstasy users also completed a higher proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to STHD ecstasy users. One-way ANOVA revealed a significant difference

between the groups in terms of the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session, $F(2, 90)= 9.48$, $p<.001$, partial eta squared=.17. Helmert contrasts showed that compared to non-ecstasy users, the combined group of short-tem high dose ecstasy users and STLD ecstasy users remembered to complete a significantly lower proportion of Karolinska fatigue questionnaires in the second half of the test-session, $p=.004$. Furthermore, relative to STHD ecstasy users, STLD ecstasy users completed a significantly higher proportion of Karolinska fatigue questionnaires in the second half of the test-session, $p=.002$. Pairwise comparisons adjusted by Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users (M=70.62, SD=28.97) completed a significantly greater proportion of Karolinska fatigue questionnaires in the second half of the test-session compared to STHD ecstasy users (M=39.85, SD=30.46), $p<.001$. STLD ecstasy users (M=66.81, SD=23.07) also completed a significantly higher proportion of Karolinska fatigue questionnaires in the second half of the test-session compared to STHD ecstasy users, $p=.002$. There was no significant difference between non-ecstasy users and STLD ecstasy users in terms of the proportion of Karolinska fatigue questionnaires completed in the second half of the test-session, $p=.59$.

Inspection of the data in Table 7.8 reveals that over the entire test-session, non-ecstasy users and STLD ecstasy users completed a higher proportion of Karolinska fatigue questionnaires than STHD ecstasy users. Overall completion rates were comparable between non-ecstasy users and STLD ecstasy users. One-way ANOVA revealed that there was a significant difference between the groups in terms of the overall proportion of Karolinska fatigue questionnaires during the entire test-session, $F(2,90)=5.46$, $p=.01$, partial eta squared=.11. Helmert contrasts showed that non-ecstasy users completed a significantly larger proportion of Karolinska fatigue questionnaires during the entire test-session compared to the combined group of STHD ecstasy users and STLD ecstasy users, $p=.02$. Short-term lose dose ecstasy users also remembered to complete a significantly larger proportion of Karolinska fatigue questionnaires during the entire test-session compared to STHD ecstasy users, $p=.02$. Pairwise comparisons adjusted for Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users (M=79.38, SD=19.14) completed a significantly larger proportion of Karolinska fatigue questionnaires during the entire test-session compared to STHD ecstasy users (M=63.61, SD=19.23), $p=.002$. The pairwise comparison between STHD ecstasy users and STLD ecstasy users (M=77.09, SD=17.76) approached statistical significance, $p=.02$ such that STHD ecstasy users

completed fewer Karolinska fatigue questionnaire during the entire test-session. There was no significant difference in the overall proportion of Karolinska fatigue questionnaires completed during the entire test-session between non-ecstasy users and STLD ecstasy users, p=.63

7.6 Discussion

Ecstasy use has been associated with deficits on a range of laboratory-based PM tasks. However, the extent to which the typical dose of ecstasy per session affects PM performance has not been fully explored. The aims of Studies 1 and 2 were to determine whether the long and short-term typical dose of ecstasy per session can predict performance on laboratory PM tasks. The laboratory PM tasks used in this study (the F1 event-based PM task, the Karolinska fatigue PM task and the long-term delayed recall PM task) have been used previously to investigate PM deficits in drug users (Hadjiefthyvoulou et al., 2011a).

The overall findings are at least in part consistent with previous studies (Hadjiefthyvoulou et al., 2011a; Heffernan et al., 2001a; Montgomery & Fisk, 2007; Rendell et al., 2007) and support the view that ecstasy use is associated with deficits in short-term time- and event-based PM. In Study 1, ecstasy users (the combined group of LTHD ecstasy users and LTLD ecstasy users) completed a significantly lower proportion of Karolinska fatigue questionnaires than non-ecstasy users during the second half of the test-session. In Study 2, STHD ecstasy users made significantly more errors on Trial 3 of the F1 event-based PM task compared to non-ecstasy users. Similar ecstasy-related deficits have been documented in the literature (Hadjiefthyvoulou et al., 2011a). However, in contrast to previous research (Hadjiefthyvoulou et al., 2011a), no long-term time-based PM deficits were found in ecstasy users in Study 1 or Study 2.

Long-term dose of ecstasy per session was not associated with any of the laboratory PM measures used. That is, LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users performed comparably on laboratory measures of event- (F1 event-based PM task) and time-based (the long-term delayed recall task) PM. It may be that access to a larger number of ecstasy users which would allow for the use of correlational analyses might be a more powerful technique with which to investigate dose-related effects compared to simply categorising users on the basis of a median split. Unfortunately, the number of ecstasy users in the present study was not sufficient to use a correlational approach and using a median split to dichotomise long and short-term average dose of ecstasy per session clearly results in a substantial loss

of precision. Furthermore, by implication, the use of median splits is problematic in that they are typically accompanied with a considerable loss of statistical power (Federov, Mannino & Zhang, 2009; Naggara et al., 2011). Following the collection of additional data, correlational analyses will be used in later empirical work where we will attempt to more systematically evaluate dose related effects.

In terms of short-term dose-related effects, STHD ecstasy users, STLD ecstasy users and non-ecstasy users performed similarly on the F1 event-based PM task and the long-term delayed recall PM task. However, an important aspect of the present findings was the presence of apparent short-term dose-related effects of ecstasy use on short-term time-based PM performance. Short-term average dose of ecstasy per session was directly related to adverse outcomes on the Karolinska fatigue PM task. Relative to STHD ecstasy users, STLD ecstasy users completed significantly more Karolinska fatigue questionnaires during the second half of the test-session. Overall completion rate on the Karolinska fatigue PM task was also worse for STHD ecstasy users compared to STLD ecstasy users. These findings indicate that short-term trends in ecstasy dose per session (larger doses of ecstasy consumed per session in the last 12 months) may predict short-term time-based PM deficits in ecstasy users. More specifically, higher ecstasy doses per session in the 12 months prior to testing appear to be associated with short-term time-based PM deficits. It is possible that larger short-term doses of ecstasy per session give rise to increased MDMA plasma concentrations in the brain. Morefield and colleagues (2011) indicate the consumption of larger dose of ecstasy per session elevate MDMA plasma concentrations for a number of hours. As a result, MDMA exposure in the brain is likely to be increased thereby enhancing ecstasy's neurotoxic potential and accounting for the short-term time-based PM deficits observed (Morefield et al., 2011).

Despite the apparent short-term dose-related effects of ecstasy use on short-term time-based PM performance, a number of limitations need to be acknowledged. One possibility is that apparent short-term dose-related effects of ecstasy use on PM may merely represent a post intoxication effect. That is, some participants may have used ecstasy in the few days prior to the test-session and thus, this may have affected their short-term time-based PM performance. The median period of abstinence for STHD ecstasy users was 3.50 weeks and for STLD ecstasy users was 52.00 weeks.

However, a total of five out of the 22 STHD ecstasy users who completed the Karolinska fatigue PM task had in fact used ecstasy within the seven days prior to the test-session. It is therefore possible that the short-term dose-related effect which was observed in Study 2 was driven by a post-intoxication effect. Nonetheless, when these individuals were excluded from the analyses, the abovementioned group differences on the Karolinska time based PM task remained statistically significant. (see Appendix 3 for inferential statistics where individuals who had consumed ecstasy in the seven days prior to the test-session are excluded from the analyses.).

Further examination of the median average dose of ecstasy per session for the STLD ecstasy user group shows that individuals in this group consumed very low doses of ecstasy per session. In fact, ecstasy dose per session was sufficiently low enough to suggest that this group was predominantly composed of previous ecstasy users (i.e., abstinent for at least six months and many for a year or more). In comparison, the STHD ecstasy user group appeared to contain more individuals who had regularly used during the previous 12 months. Thus, to an extent, the present study is in fact comparing current ecstasy users and previous ecstasy users. As a result, it may not be that the observed effects are attributable to short-term trends in the average dose of ecstasy per session. Rather, it could be argued that the current findings reflect an effect of recent ecstasy use whereby current ecstasy users perform worse than previous ecstasy users and non-ecstasy users on short-term time based PM tasks.

One of the main methodological limitations of the present investigation is related to the widespread frequency of polydrug use among ecstasy users. In both studies (Study 1 & Study 2), a large proportion of ecstasy users also consumed cannabis and cocaine, thereby increasing the possibility that the apparent short-term ecstasy-related effects on time based PM that were observed might be attributable to any one of these three major illicit drugs. For example PM impairments have been found in both cannabis (Hadjiefthyvoulou et al., 2011a; Hadjiefthyvoulou et al., 2011b; McHale & Hunt, 2008) and cocaine (Hadjiefthyvoulou et al., 2011a; 2011b) users. In addition, the observed deficits may reflect cocktail effects associated with the joint consumption of ecstasy, cannabis and cocaine. This methodological issue is further complicated by the absence of a polydrug control group. The inclusion of

cannabis-only and cocaine-only control groups would have been desirable although a much larger cohort would have been needed to do this. The difficulty here is that a large proportion of cannabis users and cocaine users also use other illicit drugs. Moreover, in cases where cannabis users or cocaine users do not use other illicit substances, these groups commonly consume alcohol and tobacco. This is problematic given that PM deficits have been found in excessive alcohol users (Heffernan & Bartholomew, 2006) and cigarette smokers (Heffernan et al., 2005). As such obtaining a true sample of cannabis-only and in particular cocaine-only users can be very difficult. Following the collection of additional data, further empirical work will attempt to control for the aforementioned factors using correlational analyses.

Another methodological issue that should be acknowledged is that the groups in both studies differed significantly in terms of age. In Study 1, non-ecstasy users were significantly younger than LTLD ecstasy users and in Study 2, non-ecstasy users were significantly younger than STHD ecstasy users and STLD ecstasy users. Despite this, closer examination of the mean data for all groups reveals that the age differences were very small. In fact, all groups were in their early twenties. This is significant given that age differences in PM do not emerge until late adulthood. In fact, it has been suggested that PM ability does not decline significantly until a person is in their 50's or 60's (Uttl, 2008). It is therefore unlikely that the age-related group differences observed here give rise to PM differences in their own right.

There was also a significant difference in years of education between LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users. However, differences in the number of years of education between the groups tell us relatively little about their intelligence. With this in mind, it is important to consider the fluid intelligence data (Raven's Progressive Matrices) which may be a more accurate predictor of PM performance. Crucially, there were no significant difference between these groups in terms of fluid intelligence (Raven's Progressive Matrices) and thus there is no reason to suggest that differences in years of education would give rise to PM differences. Aside from differing on age and years of education, it is possible that the groups differed on some other pre-existing condition predating their drug use or in terms of some other lifestyle variable. Thus, there may be a number of potential confounds,

some of which might be currently unknown which may have had an impact on the results reported in Study 1 and Study 2.

To conclude, long-term dose of ecstasy per session was not related to any PM outcomes. However, the relationship between the typical long-term dose of ecstasy per session and PM performance has received little attention previously. Our later empirical work (Chapter 11) will address this issue further. Short-term trends in the average dose of ecstasy consumed in a single session in the previous 12 months appear to be linked to short-term time-based PM deficits. However, this evidence is not conclusive in light of very low ecstasy consumption of the STLD user group in the previous 12 months. Nonetheless, the findings on the whole do show an overall ecstasy-related effect such that ecstasy users were significantly impaired on short-term time- and event-based PM tasks. Thus, larger doses of ecstasy consumed in recent sessions appear to be may exacerbate the neurotic effects of ecstasy by increasing MDMA plasma concentrations in the brain.

Chapter 8: The effects of concurrent alcohol and ecstasy use on prospective memory performance

Chapter 8 investigates the effects of concurrent alcohol and ecstasy use on Prospective Memory (PM) performance. Median splits were used to dichotomise long- (Study 1) and short-term (Study 2) concurrent alcohol and ecstasy use. Two concurrent alcohol user groups were created in Study 1 [long-term high alcohol (LTHA) ecstasy users and long-term low alcohol (LTLA) ecstasy users] and also in Study 2 [short-term high alcohol (STHA) ecstasy users and short-term low alcohol (STLA) ecstasy users]. Study 1 investigates the extent to which long-term concurrent alcohol and ecstasy use (typical dose of ecstasy per session averaged over the entire period of use) can predict PM performance. Study 2 explores the extent to which short-term concurrent alcohol and ecstasy use (average typical dose of ecstasy per session over the previous 12 months) is associated with PM deficits.

8.1 Introduction

The empirical work in Chapter 7 showed clear effects of ecstasy use on prospective memory (PM) performance. The long-term typical dose of ecstasy per session was not associated with performance on event- or time-based measures of PM. However, higher average typical dose of ecstasy in the 12 months prior to the test-session was associated worse performance on the Karolinska fatigue PM task. One of the key limitations of these findings, and indeed the drug-related literature in general is that ecstasy users typically use ecstasy alongside other drugs. Therefore, it is very difficult to determine whether the effects observed are attributable to the use of ecstasy, other drugs or due to a cocktail effect of several drugs. Alcohol is a licit drug that is commonly used concurrently with ecstasy (Barrett, Darredeau & Pihl, 2006; Grov, Kelly & Parsons, 2009; Fisk, Montgomery & Murphy, 2009). Riley, James, Gregory, Dingle and Cadger (2001) propose that approximately 85% of those individuals who attend rave events and consume ecstasy also use alcohol concurrently. This therefore makes it difficult for researchers to conclude that effects found in concurrent alcohol/ecstasy users are entirely attributable to ecstasy use alone (Gouzoulis-Mayfrank & Daumann, 2006). The aim of the current Chapter is to investigate the

effects of short- and long-term concurrent alcohol and ecstasy use on PM performance.

The use of alcohol has been linked to both acute and long-term deficits in PM. In one particular study, Leitz, Morgan, Bisby, Rendell & Curran (2009) used the Virtual Week task (Rendell & Craik, 2000; see section 5.2 for a full description of this task) and found that the acute effects of alcohol intoxication are detrimental to performance on regular and irregular event- and time-based PM tasks. Similar findings were reported by Paraskevaides et al. (2010) who found that acute alcohol consumption impaired PM performance for event-based PM tasks on the Virtual Week task. More recently, Montgomery, Ashmore and Jansari (2011) used The JAAM assessment (Jansari et al., 2004; see section 5.2 for a full description of this task) and found that a low dose of alcohol (0.4g/kg alc) impaired PM performance on event-and time-based PM tasks. Paraskevaides et al. (2010) argue that alcohol use makes it difficult for people to combine fragments of the past from episodic memory in order to form a new combination of episodic future thoughts (a form of thinking whereby an individual projects an image of themselves into the future to pre-experience an event).

Aside from the acute effects of alcohol use on PM performance, deficits in this aspect of everyday memory have been observed in currently abstinent individuals. For example, a number of studies claim that high dose alcohol users report more errors in their short- and long-term PM abilities compared to low dose alcohol users (Heffernan & Bartholomew, 2006; Heffernan et al., 2002; Heffernan et al., 2006). Despite these findings, some studies have failed to show PM deficits in alcohol users. For example, Heffernan et al. (2010a) did not find evidence of self-reported PM lapses in teenage binge drinkers. One possible explanation for the discrepancy between the findings is that Heffernan and colleagues (2010a) screened out individuals who reported the use of illicit drugs known to adversely affect PM performance (i.e., cannabis and ecstasy). Previous studies where self-reported deficits in PM were found (Heffernan & Bartholomew, 2006; Heffernan et al., 2002; Heffernan et al., 2006) had not controlled for this factor. As a result these studies may merely reflect an effect of alcohol, cannabis and/or ecstasy use on PM. Moreover,

these findings may represent a cocktail effect of licit (alcohol) and illicit (cannabis, cocaine or ecstasy) substance use on PM performance.

Alcohol-related deficits in PM have also been observed on laboratory-based measures. Heffernan et al. (2010a) investigated PM performance in teenage binge drinkers using the Prospective Remembering Video Procedure (PRVP). The PRVP involves a 10-minute video clip of footage from a shopping centre. Participants are shown a range of shopping related material including shop fronts, passersby and retail stores. Prior to watching the video-clip, participants are provided with instructions relating the particular action/items associated with specific locations (e.g., when you reach the store Dixons, note how much a Playstation 2 costs). Participants are required to (prospectively) recall and note each location action/item association on a response sheet. There are 18 location action/item associations in total and one point is awarded for each association correctly recalled. Heffernan and colleagues (2010a) found that excessive drinking in teenagers was linked to poor PM performance on the PRVP. In addition, the increased number of units of alcohol consumed each week correlated significantly with worse PM performance on the PRVP. This finding is particularly significant in that it might show a dose-related effect of alcohol use on PM performance. More recently, Griffiths et al. (2012) investigated PM in individuals with alcohol dependence. PM performance was compared in 24 individuals with alcohol dependence (who had completed a 7-10 day assisted withdrawal programme to eliminate possible effects of acute intoxication) and 24 social drinkers with no self-reported history of alcohol dependence. The Virtual Week task (Rendell & Craik, 2000) was used as an objective measure of PM and individuals with alcohol dependence performed significantly worse than social drinkers on event-based PM tasks. Moreover, event-based PM performance was significantly negatively correlated with level of alcohol dependence and the number of units of alcohol consumed each week. These findings are consistent with Heffernan et al. (2010a) and lend support to the proposition that higher doses of alcohol are related to poorer performance on PM tasks.

The exact mechanisms which underpin PM deficits in alcohol users are unclear. However, one possible reason is that alcohol inhibits prefrontal lobe functioning (Wendt & Risberg, 2001). This is significant given that the prefrontal

region is implicated in PM tasks (Momennejad & Haynes, 2012; Simons et al., 2006). Evidence from animal studies shows that chronic alcohol consumption reduces the number of cholinergic neurons in the basal forebrain. This change may in turn lead to reduced hippocampal function (Garcia Moreno et al., 2001). Further data from animal studies shows that binge doses of alcohol leads to a disruption in the growth of new brain cells which ultimately induces a long-term deficit in hippocampal structure and functioning (Herrera et al., 2003; Nixon & Crews, 2002). This is important in the context of the present thesis in that hippocampal functioning is necessary for normal functioning on PM tasks (Adda et al., 2008; Martin et al., 2007). As such, this abnormality may account for some of the PM deficits that have been observed in alcohol users. Alcohol use is also suggested to be damaging to cerebral white matter which is involved in binding important regions together in the brain. These regions include the frontal and the limbic systems which have been shown to be fundamental in forming new memories (Oscar-Berman & Marinkovic, 2007). Once again, this might have important implications for PM performance. For example, if an individual is unable to form memories for a future intention (i.e., a PM task), their PM performance is likely to be impaired. Alternative explanations might argue that alcohol-related impairments in PM are mediated by neurotransmitters such as 5-HT which is known to be important for mnemonic processes (Hunter, 2000; Spoont, 1992).

Overall, there is a wide body of research that suggests that excessive alcohol consumption is associated with self-reported and laboratory-based deficits in PM. There is also substantial evidence, which indicates that the use of ecstasy can impair PM performance (Hadjiefthyvoulou et al 2011a; 2011b). This literature is documented in Chapter 6 (section 6.2). However, one avenue of investigation which remains to be thoroughly explored is the effect of concurrent alcohol and ecstasy use on PM performance. This is an important topic of investigation given that the co-abuse of alcohol and ecstasy is suggested to enhance ecstasy-mediated long-term neurotoxicity (Izco et al., 2007).

In humans, the concurrent use of alcohol and ecstasy has been associated with increased alertness (Dumont et al., 2010), impaired psychomotor function (Dumont et al., 2010), poor general health, confusion, moodiness (Fisk, Murphy, Montgomery &

Hadjiefthyvoulou, 2011) and enhanced feelings of euphoria (relative to the use of ecstasy alone) (Hernandez-Lopez et al., 2002). With regard to acute intoxication, the co-administration of alcohol and ecstasy does not appear to increase deficits on executive, memory, psychomotor, visuomotor, visuospatial or attention functions beyond that of the use of ecstasy alone (Dumont et al., 2008). Nonetheless, a significant limitation of this study was that the doses of alcohol and ecstasy that were investigated were not representative of the typical doses which are consumed by concurrent alcohol and ecstasy users (Cassel, Hamida & Jones, 2008). Further harmful alcohol-ecstasy interactions have been found. Upreti, Eddington, Moon, Song & Lee (2009) found that the co-administration of ethanol and MDMA in rats increased hepatocellular damage to levels that were not found following the administration of ethanol or MDMA alone.

A number of animal-based studies have linked concurrent alcohol and ecstasy consumption to cognitive impairments including problems in memory and learning (Hernandez-Rabaza et al., 2010; and Vidal Infer, Aguilar, Miñarro & Rodriguez-Arias, 2012). Hernandez-Rabaza et al. (2010) investigated the effects of repeated exposure to ecstasy, which was either given alone or together with ethanol, on memory performance. Two weeks after a specific drug-treatment period (ecstasy alone, alcohol and ecstasy together or control), rats were trained in a radial arm maze. The radial arm maze is a laboratory task that involves different aspects of spatial and working memory, loading heavily on the hippocampus and prefrontal cortex, respectively. Crucially, only rats who had received alcohol and ecstasy concurrently displayed long-term deficits in spatial orientation and working memory performance. It is important to note that the concurrent ethanol and ecstasy effect was observed at doses of ethanol and ecstasy that did not impair cognitive ability when given separately. Thus, it appears that the risk of developing visuo-spatial and working memory impairments is heightened when ethanol and ecstasy are administered together. These deficits were related to neuronal loss and microgliosis in the dentate gyrus region of the hippocampus. The impairment that was observed in relation to working memory performance is of particular interest in light of research that has associated PM performance with problems with the central executive. These findings are also important given the involvement of the hippocampus (Adda et al., 2008; Martin et al., 2007) and the prefrontal cortex (Momennejad & Haynes, 2012; Simons,

et al., 2006) in PM tasks.

Vidal Infer et al. (2012) reported similar findings in mice. Adolescent mice were administered with either ethanol and MDMA, ethanol alone, MDMA alone or a saline control solution during a treatment period which simulated a binge pattern characteristic of that seen in human adolescents and young adults. At 64 days post-treatment, the mice were initiated into the Hebb-Williams maze. The Hebb-Williams maze is a complex spatial learning test which is used to detect abnormalities in cognitive functioning. A number of different mazes are used, each of varying difficulty. The mice must navigate from a wet "start" box to a dry "goal" box as quickly as possible. Acquisition criterion scores (completion of the task in under 60 seconds for two consecutive trials), total latency scores (the sum of the latencies in all trials for each individual maze), latency for reaching the goal on trial 8 and error scores (error scores were awarded when mice entered an error zone in each maze) were all recorded. The authors found that concurrent ethanol and MDMA administration in adolescent mice had long-lasting effects on learning and memory. Mice that received ethanol and MDMA both alone and together took longer to reach the end goal on the Hebb-Williams maze compared to saline treated counterparts. In addition, mice that were treated with ethanol alone or alongside MDMA recorded longer latency scores and also needed more trials to reach the acquisition criterion score compared to saline treated counterparts. Interestingly, MDMA was linked with a decrease in dopamine striatal volume and this effect was accentuated by the concurrent use of alcohol. Impairments of the dopamine system which result from the concurrent use of alcohol and ecstasy can have important implications for PM performance. Goto and Grace (2008) explain that dopamine is necessary for transporting hippocampal-based retrospective information to the prefrontal cortex and in the further processing of information to effect preparation of future intentions. These links between dopamine and PM-related brain regions increase the likelihood that the concurrent use of alcohol and ecstasy may impair PM performance to a greater degree that alcohol and/or ecstasy use alone.

To date, no research has attempted to directly investigate the effects of concurrent alcohol and ecstasy use on cognitive performance. The present investigation used a timeline technique similar to that adopted in Chapter 7 (also see Bedi & Redman,

2008b; Medina et al., 2005) to investigate effects of concurrent alcohol and ecstasy use on PM performance. In addition providing an estimate of typical dose of ecstasy per session and the frequency of use (number of times per week, month, etc), participants were asked to provide an estimate of the typical number of units of alcohol consumed per session when using the drug. This was done for each year that an individual had used ecstasy (Study 1) and for each month during the 12 months prior to the test-session (Study 2). These data were then be used to calculate the average number of units of alcohol that were typically consumed while taking ecstasy in a representative session. These averages were computed long term, i.e., averaged annually over the entire period of use, and short term, i.e., averaged monthly over the previous 12 months. Median splits were used to dichotomise these long- (Study 1) and short-term (Study 2) measures of concurrent alcohol use. Two concurrent alcohol user groups were created in Study 1 [long-term high alcohol (LTHA) ecstasy users and long-term low alcohol (LTLA) ecstasy users] and in Study 2 [short-term high alcohol (STHA) ecstasy users and short-term low alcohol (STLA) ecstasy users]. A control group of non-ecstasy users was included in the analyses (see Section 8.2 and 8.4 for full description). Groups were compared on a range of demographical and background variables including age, intelligence, years of education, daytime sleepiness (Epworth Sleepiness Scale), gender, cigarette and alcohol consumption, arousal, anxiety and depression. Study 1 investigates the extent to which long-term concurrent alcohol and ecstasy use (typical dose of ecstasy per session averaged over the entire period of use) can predict PM performance. Study 2 explores the extent to which short-term concurrent alcohol and ecstasy use (average typical dose of ecstasy per session over the previous 12 months) is associated with PM deficits.

Study 1

8.2 Method

Participants

Twenty long-term concurrent high-alcohol ecstasy users (LTHA; 13 males), 20 long-term concurrent low-alcohol ecstasy users (LTLA; 13 males) and 44 non-ecstasy users (16 males) took part in the investigation (for demographic variables, see Table 8.1). The gender composition did differ significantly between the groups, $\chi^2(2)=6.87$, $p=.03$. There were more females (n=28) than males (n=16) in the non-ecstasy users group. There were more males (n=13) than females (n=7) in the LTHA ecstasy user group. There were also more males (n=13) than females (n=7) in the LTLA ecstasy users group. Participants were recruited via direct approach to university students. All participants were university students attending Liverpool John Moores University (LJMU) or the University of Central Lancashire (UCLAN). None had participated in the studies reported in the previous Chapter. Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to test-session (the mean period of abstinence for LTHA ecstasy users was 35.94 weeks, median=10.00 weeks; the mean period of abstinence for LTLA ecstasy users was 23.08 weeks, median=4.00 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing. The present study was approved by the ethics committees of the University of Central Lancashire and Liverpool John Moores University in accordance with the guidelines of the British Psychological Society.

Materials

Patterns of ecstasy and other drug use were obtained via a background drug use questionnaire (Montgomery et al., 2005, see Appendix 1 for a copy of this questionnaire). For the major illicit drugs, the same measures of long-term drug use (annual average dose per session and frequency of use) were collected as indicated in the previous Chapter. In addition, estimates of the typical dose of alcohol consumed in a single session concurrently with ecstasy were recorded for each year since ecstasy use commenced. The mean of these annual estimates was taken to produce an overall long-term average representing the typical number of units of alcohol consumed in a single session along with ecstasy. The current use of cigarettes and alcohol were also

assessed. The Raven's Progressive Matrices test (Raven et al., 1998) was used as a measure of fluid intelligence. Daytime sleepiness was measured via the Epworth Sleepiness Scale (Johns, 1991; see Empirical Chapter 1, section 7.2 for a detailed description of this measure. See Appendix 2 for a copy of this questionnaire).

Four laboratory measures of PM were administered including the F1 event-based PM task (Hadjiefthyvoulou et al., 2011a), the Long Term recall PM task (Hadjiefthyvouolou et al., 2011a), the fatigue PM task (Hadjiefthyvoulou et al., 2011a) and the Cambridge PM test (CAMPROMPT; Wilson et al., 2005). See Chapter 5, section 5.3 for a full description of this measure. A computer using MS-DOS was used for the F1 event-based PM task. Full descriptions of all laboratory measures of PM can be found in Chapter 5.

Procedure

Participants were informed of the general purpose of the experiment and verbal informed consent was obtained. Background questionnaires assessing age, years of education, general health and other relevant lifestyle variables (arousal, anxiety and depression, Daytime sleepiness) were administered first and in a counterbalanced order. The Raven's Progressive Matrices task, the F1 event-based PM task, the Long-term recall PM task and the CAMPROMPT were then administered in a counterbalanced order. The Karolinska fatigue PM task was administered throughout the test-session. Finally, the background drug use questionnaire was administered.

All tests were administered under laboratory conditions. Participants were fully debriefed and given the opportunity to ask any questions about the study prior to leaving the laboratory. Participants were paid £20 in store vouchers for their participation.

Design/Statistics

A median split was used to dichotomise long-term concurrent alcohol and ecstasy use. For each year, the typical number of units of alcohol consumed in a single session whilst using ecstasy was recorded. The resulting figures were averaged over the entire period that an individual had used alcohol and ecstasy concurrently (intervening years during which the drug was not used are coded as zero) producing an annual average

and thus create two user groups (LTHA ecstasy users and LTLA ecstasy users). The median for long-term concurrent alcohol and ecstasy use was 11.03 units. Participants who, on average, consumed 11.03 or more units of alcohol per session of ecstasy use were classified as LTHA ecstasy users and those that consumed less than 11.03 units of alcohol per session of ecstasy use were classified as LTLA ecstasy users. The high and low alcohol groups together with a non-ecstasy user group constituted the three levels of the between participant IV.

All measures were analysed using a between-participant design with user group as the independent variable (LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users). Age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale Score, arousal, anxiety and depression were included as background measures. Any group differences on these background variables were investigated using one-way ANOVA. Total ecstasy, cannabis and cocaine consumption, long-term average dose of ecstasy, cannabis and cocaine per session, long-term concurrent alcohol and ecstasy use (the typical number of units of alcohol consumed per session of ecstasy use) long-term (average weekly consumption averaged over lifetime for ecstasy, cannabis and cocaine) frequency of ecstasy, cannabis and cocaine use, and the duration of ecstasy, cannabis and cocaine use were included as background drug use variables.

Data for total lifetime ecstasy, cannabis and cocaine use, long-term average dose of ecstasy, cannabis and cocaine per session, long-term concurrent alcohol and ecstasy use, the duration of ecstasy, cannabis and cocaine use, the long-term average frequency of ecstasy, cannabis and cocaine use and the current frequency of ecstasy, cannabis and cocaine use were not normally distributed. This was characterised by skew or kurtosis associated with z values exceeding 3.29, $p<.001$. As a result non-parametric analyses were used (Tabachnick & Fidell, 2001).

8.3 Results

Demographical and Background Variables

The scores for the demographical variables and background variables of age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression are set out in Table 8.1. LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users were compared on a number of background drug use variables and these data are shown in Table 8.2.

Table 8.1 Demographical variables of long-term high alcohol ecstasy users, long-term low alcohol ecstasy users and non-ecstasy users.

	LTHA ecstasy users		LTLA ecstasy users		Non-ecstasy users		p
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
Age (years)	21.80 (1.70)	20	21.55 (2.39)	20	20.09 (2.12)	44	.004**
Raven's Progressive Matrices (max 60)	44.75 (6.25)	20	46.38 (4.66)	16	44.45 (7.98)	42	.64
Years of education	16.03 (1.74)	20	15.53 (1.93)	19	14.55 (1.81)	42	.009**
Alcohol (units per week)	23.59 (22.04)	17	10.31(8.63)	18	9.96 (12.11)	42	.004**
Cigarettes per day	5.91 (4.10)	17	6.00 (3.74)	8	6.95 (2.93)	8	.82
Epworth Sleepiness Score	6.25 (2.92)	20	8.73 (3.93)	17	6.73 (3.07)	40	.08
Arousal	18.94 (5.62)	18	19.47 (3.93)	17	19.62 (3.80)	39	.86
Anxiety	10.94 (2.90)	18	13.00 (3.84)	17	11.26 (2.83)	38	.10
Depression	11.89 (2.70)	18	13.35 (3.10)	17	12.54 (2.49)	39	.28

**$p<.01$

One-way ANOVA revealed there was a significant age difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users. Tukey's post hoc test showed that non-ecstasy users were significantly younger than both LTHA ecstasy users and LTLA ecstasy users. There was no significant difference between LTHA ecstasy users and LTLA ecstasy users in terms of age.

The group difference was significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of years of education. Tukey's post hoc test showed that non-ecstasy users had studied for a significantly shorter period of time compared to LTHA ecstasy users. There was no significant difference between non-ecstasy users and LTLA ecstasy users or LTHA ecstasy users and LTLA ecstasy users in terms of number of years of education.

There was also a significant difference in the typical number of units of alcohol consumed per week between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users. Tukey's post hoc test showed that LTHA ecstasy users consumed significantly more alcohol per week compared to LTLA ecstasy users and non-ecstasy users. There was no significant difference in the typical number of units of alcohol consumed per week by LTLA ecstasy users and non-ecstasy users. A series of one-way ANOVAs revealed that the groups did not differ significantly in terms of intelligence, cigarette consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression (see Appendix 4 for detailed statistical analyses related to background variables).

Table 8.2 Background drug use variables of long-term high alcohol ecstasy users, long-term low alcohol ecstasy users and non-ecstasy users.

	LTHA ecstasy users					LTLA ecstasy users					Non-ecstasy users					p
	Median	Min.	Max.	Int. Range	n	Median	Min.	Max.	Int. Range	n	Median	Min.	Max.	Int. Range	n	
Total prior consumption																
Ecstasy (tablets)	93.50	6.00	686.00	352.75	20	32.00	1.00	1078.00	117.25	20	-	-	-	-	-	.04*
Cannabis (joints)	767.00	2.00	21240.00	4863.00	19	1062.00	1.00	5128.00	1523.00	14	237.00	14.00	1888.00	1644.25	8	.48
Cocaine (lines)	120.50	4.00	1288.00	329.25	18	80.00	6.00	994.00	415.17	16	23.50	1.00	46.00	-	2	.55
Long-term average dose per session																
Ecstasy	3.00	.67	6.67	1.72	20	2.00	.86	4.50	1.93	20						.04*
Cannabis	1.90	.60	10.00	5.04	18	1.67	.31	5.25	.79	15	1.63	.40	4.00	1.25	12	.41
Cocaine	4.67	1.00	20.00	3.70	19	3.25	.08	7.67	2.14	15	-	-	-	-	1	.02*
Alcohol consumed concurrently with ecstasy (units)	19.96	11.25	35.00	10.00	20	6.01	.00	10.08	5.55	20						<.001***
Duration of use (number of weeks)																
Ecstasy	168.00	28.00	412.00	142.25	20	188.00	.00	468.00	293.32	18	-	-	-	-	-	1.00
Cannabis	272.50	128.00	568.00	194.54	18	267.88	56.00	467.88	147.00	15	121.50	14.00	472.00	223.92	12	.04*
Cocaine	207.00	32.00	361.00	177.00	18	159.14	.00	488.00	228.00	13	78.00	4.00	152.00	-	2	.31
Long-term frequency of use (number of occasions of use per week)																
Ecstasy	.17	.04	.72	.30	20	.07	.02	1.00	.22	20	-	-	-	-	-	.20
Cannabis	1.31	.02	7.00	4.23	18	.23	.00	7.00	2.66	15	.33	.01	3.33	2.09	12	.19
Cocaine	.10	.02	1.33	.14	19	.19	.01	10.00	.40	15	-	-	-	-	1	.39

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

Inferential statistics for those outcomes in Table 8.2 that were not significant are reported in Appendix 4. Similarly all other pairwise differences that are not explicitly referred to below are non-significant and the inferential statistics are presented in Appendix 4.

The data in Table 8.2 shows that LTHA ecstasy users had consumed more ecstasy tablets over their lifetime compared to LTLA ecstasy users with Mann-Whitney U test showing that this effect was statistically significant, U=123.50, p=.04. In relation to average typical dose per session, LTHA ecstasy users typically consumed more ecstasy tablets compared to LTLA ecstasy users. Once again, this group difference was statistically significant, U=125.50, p=.04. Consistent with the manner in which the groups were constructed, in relation to long-term concurrent alcohol and ecstasy use, the median data in Table 8.2 shows that LTHA ecstasy users consumed significantly more alcohol per session of ecstasy use relative to LTLA ecstasy users, U=.00, p<.001. While LTHA ecstasy users had used ecstasy more recently than LTLA ecstasy users, this trend was not significant. Group differences on the duration of ecstasy use, long-term average frequency of ecstasy use were less evident and were also non-significant.

Table 8.2 shows that LTHA ecstasy users and LTLA ecstasy users had been using cannabis for a similar duration of time. Both concurrent alcohol and ecstasy groups had been using cannabis for longer than non-ecstasy users. Kruskal-Wallis test revealed that the overall group difference was significant, $\chi^2(2)=6.24$, p=.04. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) showed that LTHA ecstasy users had used cannabis for a significantly longer duration of time compared to non-ecstasy users, U=50.00, p=.01. Although it is clear from Table 8.2 that lifetime cannabis use and the long-term average frequency of cannabis use varied substantially between the groups, these trends were not statistically significant. Group differences on long term average cannabis dose and period of abstinence were less evident and again non-significant

For the cocaine use measures listed in Table 8.2, since there were only one or two non-ecstasy cocaine users, comparisons were restricted to the two concurrent alcohol and ecstasy user groups. On this basis, the median data shows that LTHA ecstasy users consumed more cocaine per session and had used cocaine more recently than

LTLA ecstasy users. Mann-Whitney U tests revealed that both group differences were significant, U=77.00, *p*=.02, U=62.50, *p*=.014, respectively. Although LTHA ecstasy users had higher levels of total lifetime cocaine consumption and had been using cocaine for longer that LTLA ecstasy users, these trends were not significant.

Laboratory-based measures

Outcomes for the laboratory-based measures of PM for LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users are summarised in Table 8.3.

Table 8.3 Means, Standard Deviations (SD), Median (Med.), Minimum (Min.), Maximum (Max.) and Interquartile Range (Int. Range) scores for long-term high alcohol ecstasy users, long-term low alcohol ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall task, the Karolinska fatigue PM task and the Cambridge PM test.

	LTHA ecstasy users n=20					LTLA ecstasy users n=20					Non-ecstasy users n=44					p
	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	
F1 event-based PM task																
Trial 1 Errors	.45 (1.00)	.00	.00	3.00	.00	.61 (1.09)	.00	.00	3.00	1.25	.14 (.65)	.00	.00	3.00	.00	.05
Trial 2 Errors	.15 (.67)	.00	.00	3.00	.00	.33 (.94)	.00	.00	3.00	.00	.00 (.00)	.00	.00	.00	.00	.11
Trial 3 Errors	.10 (.31)	.00	.00	3.00	.00	.28 (.83)	.00	.00	3.00	.00	.05 (.22)	.00	.00	1.00	.00	.58
Total Errors	.70 (1.53)	.00	.00	6.00	1.00	1.22 (2.32)	.00	.00	8.00	2.00	.19 (.67)	.00	.00	3.00	.00	.06
Long-term delayed recall PM task																
Total number of recall tests returned (max of 3)	.95 (1.18)	.00	.00	3.00	2.00	.70 (1.17)	.00	.00	3.00	2.00	1.41 (1.42)	.00	.00	3.00	3.00	.11
Karolinska fatigue PM task																
Percentage completed in first half of test-session	85.04 (16.29)	84.42	50.00	100.00	23.75	84.91 (14.71)	80.00	60.00	100.00	20.00	91.31 (16.00)	100.00	20.00	100.00	20.00	.09
Percentage completed in second half of test-session	40.75 (34.61)	36.67	.00	100.00	58.34	44.74 (31.90)	40.00	.00	100.00	55.00	79.92 (27.91)	100.00	.00	100.00	27.09	<.001***
Percentage completed overall	60.46 (23.36)	56.95	30.00	100.00	33.43	64.50 (20.48)	60.00	30.00	100.00	30.00	86.09 (17.53)	90.45	27.27	100.00	21.25	<.001***
Cambridge PM test																
Event-based PM performance	15.00 (3.90)	16.00	2.00	18.00	4.50	12.63 (3.70)	13.00	4.00	18.00	5.50	16.95 (1.97)	18.00	8.00	18.00	2.00	<.001***
Time-based PM performance	13.56 (4.15)	15.00	4.00	18.00	4.50	13.06 (3.53)	14.00	4.00	18.00	4.75	17.15 (1.97)	18.00	8.00	18.00	1.50	<.001***
Overall PM performance	28.56 (6.65)	28.00	12.00	36.00	10.00	25.69 (6.65)	28.00	8.00	34.00	6.00	34.15 (3.28)	36.00	20.00	36.00	2.00	<.001***

***p<.001 *Note.* n for all groups was variable due to missing data. Eighteen long-term low alcohol ecstasy users completed the F1 event-based PM task. Only 19 long-term high alcohol ecstasy users completed the long-term delayed recall PM task. Nineteen long-term low alcohol ecstasy users and 42 non-ecstasy users completed the Karolinska fatigue PM task. Eighteen long-term high alcohol ecstasy users, 16 long-term low alcohol ecstasy users and 40 non-ecstasy users completed the Cambridge PM test.

The distributions of the data for Trial 1 errors (Skew, z=8.94 and Kurtosis, z=7.73), Trial 2 errors (Skew, z=18.91 and Kurtosis, z=45.39), Trial 3 errors (Skew, z=18.20 and Kurtosis, z=49.10) and total errors (Skew, z=12.09 and Kurtosis, z=21.31) on the F1 event-based PM task, for the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed in the first half of the test-session only, Skew, z=-5.73 and Kurtosis, z=5.87) and for the CAMPROMPT (event-based PM total, Skew, z=-6.76 and Kurtosis, z=6.96, time-based PM total, Skew, z=-5.78, Kurtosis, z=3.91, overall PM, Skew, z=-5.86, Kurtosis, z=4.66) deviated significantly from normality. This was characterised by the skew and/or kurtosis z scores exceeding 3.29, $p<.001$ (Tabachnick & Fidell, 2001). Group differences were investigated via Kruskal-Wallis test with follow-up post hoc Mann-Whitney U tests (with full Bonferroni correction, adjusted alpha level=.017).

Where the distributions were normal, one-way ANOVAs were used to investigate group differences on two aspects of the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed in the second half of the test-session and overall proportion of Karolinska fatigue questionnaires completed during the first and second half of the test-session) and the long-term delayed recall PM task. ANOVAs were followed up with Helmert contrasts and pairwise comparisons.

Examination of the data in Table 8.3 reveals that LTHA ecstasy users and LTLA ecstasy users made more errors than non-ecstasy users on all trials of the F1 event-based PM task. In addition, LTLA ecstasy users made more errors than LTHA users on all trials of the F1 event-based PM task. There was no significant difference in the number of errors that were made on trial 1 of the F1 event-based PM task by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $\chi^2(2)=5.97$, $p=.051$. However, this effect did approach statistical significance. LTLA ecstasy users made significantly more errors than non-ecstasy users on trial 1 of the F1 event-based PM task, U=294.00, $p=.015$ There was no significant difference in the number of errors that were made on trial 1 of the F1 event based PM task between LTHA ecstasy users and non-ecstasy users, U=358.00, $p=.07$ or LTHA ecstasy users and LTLA ecstasy users, U=166.50, $p=.70$.

There was no significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of the numbers of errors that were made on trial 2 $\chi^2(2)=4.37$, $p=.11$ and trial 3, $\chi^2(2)=1.08$, $p=.58$ of the F1 event-based PM task. In addition, no significant difference was found in total errors made on the F1 event-based PM task by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $\chi^2(2)=5.72$, $p=.06$. Nonetheless, this effect did approach statistical significance. Post hoc tests showed that there was no significant difference between LTHA ecstasy users and non-ecstasy users, U=353.00, $p=.10$, LTLA ecstasy users and non-ecstasy users, U=284.00, $p=.019$ or LTHA ecstasy users and LTLA ecstasy users, U=162.00, $p=.61$ in terms of the overall errors made on F1 event-based PM task.

With regard to long-term time-based PM performance, the data in Table 8.3 reveals that non-ecstasy users returned more delayed recall test sheets (long-term delayed recall PM task) than both LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users also returned more delayed recall test sheets compared to LTLA ecstasy users. One-way ANOVA revealed that there was no significant difference in the number of delayed recall test sheets returned by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $F(2,80)=2.52$, $p=.11$, partial eta squared=.05.

In relation to more short-term time-based PM performance, inspection of the data in Table 8.3 shows that compared to LTHA ecstasy users and LTLA ecstasy users, non-ecstasy users successfully completed a greater number of Karolinska fatigue questionnaires during the first and second half of the test-session. Overall performance on the Karolinska fatigue questionnaire was better for non-ecstasy users compared to LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users and LTLA ecstasy users completed a similar proportion of Karolinska fatigue questionnaires during the first and second half of the test-session. In addition, overall performance on the Karolinska fatigue PM task was comparable between LTHA ecstasy users and LTLA ecstasy users.

No significant difference was found between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of the proportion of Karolinska fatigue questionnaires that were completed during the first half of the test-session, $\chi^2(2)=4.87$, $p=.09$. However, this effect did approach statistical significance. There was no significant difference in the proportion of Karolinska fatigue questionnaires

completed during the first half of the test-session by LTHA ecstasy users and non-ecstasy users, U=319.50, *p*=.08, LTLA ecstasy users and non-ecstasy users, U=290.50, *p*=.05 or LTHA ecstasy users and LTLA ecstasy users, U=184.50, *p*=.88.

One-way ANOVA revealed that there was a significant difference in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, *F*(2,78)=15.05, *p*<.001, partial eta squared=.28. Helmert contrast showed that compared to non-ecstasy users, the combined group of LTHA ecstasy users and LTLA ecstasy users completed a significantly lower proportion of Karolinska fatigue questionnaires during the second half of the test-session, *p*<.001. A further Helmert contrast revealed that there was no significant difference in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session by LTHA ecstasy users and LTLA ecstasy users, *p*=.68. Pairwise comparisons adjusted for full Bonferroni correction (significant alpha level=.017) revealed that non-ecstasy users (M=79.92, SD=27.91) competed a significantly higher proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to LTHA ecstasy users (M=44.75, SD=34.61), *p*<.001 and LTLA ecstasy users (M=40.75, SD=31.90), *p*<.001. There was no significant difference in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session by LTHA ecstasy users and LTLA ecstasy users, *p*=.68.

One-way ANOVA showed that there was a significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of the overall completion rate of Karolinska fatigue questionnaire, F(2,78)=14.07, *p*<.001, partial eta squared=.27. Helmert contrast showed that non-ecstasy users completed a significantly greater proportion of Karolinska fatigue questionnaires overall compared to the combined group of LTHA ecstasy users and LTLA ecstasy users, *p*<.001. A further Helmert contrast showed that there was no significant difference between LTHA ecstasy users and LTLA ecstasy users in terms of the proportion of Karolinka fatigue questionnaires completed overall, *p*=.53. Pairwise comparisons adjusted for full Bonferroni correction (significant alpha level=.017) revealed that non-ecstasy users (M=86.09, SD=17.53) competed a significantly higher proportion of Karolinska fatigue questionnaires overall compared to LTHA ecstasy users (M=60.46, SD=23.36), *p*<001 and LTLA ecstasy users (M=64.50, SD=20.48), *p*<.001. There was

no significant difference in the proportion of Karolinska fatigue questionnaires completed overall by LTHA ecstasy users and LTLA ecstasy users, p=.53.

Examination of the data in Table 8.3 shows that non-ecstasy users successfully completed more event-based PM tasks on the CAMPROMPT compared to LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users also completed more event-based PM tasks on the CAMPROMPT than LTLA ecstasy users. There was a significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of event-based PM performance on the CAMPROMPT, $\chi^2(2)=23.99$, $p<.001$. Non-ecstasy users were significantly better at completing event-based PM tasks on the CAMPROMPT than LTHA ecstasy users, U=222.50, p=.010 and LTLA ecstasy users, U=76.50, p<.001. No significant difference was found between LTHA ecstasy users and LTLA ecstasy users in terms of event-based PM performance on the CAMPROMPT, U=80.00, p=.03

Table 8.3 reveals that non-ecstasy users successfully completed more time-based PM tasks on the CAMPROMPT compared to LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users and LTLA ecstasy users completed a similar number of time-based PM tasks on the CAMPROMPT. A significant difference was found between the groups in terms of time-based PM performance on the CAMPROMPT, $\chi^2(2)=31.70$, $p<.001$. Non-ecstasy users completed a significantly higher number of time-based PM tasks on the CAMPROMPT than long -term high alcohol ecstasy users, U=126.00, $p<.001$, and LTLA ecstasy users, U=69.00, $p<.001$. No significant difference was found between LTHA ecstasy users and LTLA ecstasy users in terms of time based PM performance on the CAMPROMPT, U=122.50, p=.46

In terms of overall PM performance on the CAMPROMPT, the data in table 8.3 indicates that non-ecstasy users performed better than LTHA ecstasy users and LTLA ecstasy users. In addition, overall performance on the CAMPROMPT was slightly worse for LTLA ecstasy users compared to LTHA ecstasy users. There was a significant group difference in overall PM performance on the CAMPROMPT, $\chi^2(2)=33.01$, $p<.001$. Overall PM performance on the CAMPROMPT was significantly higher for non-ecstasy users compared to LTHA ecstasy users, U=136.50 $p<.001$, and LTLA ecstasy users, U=41.00, $p<.001$. There was no

significant difference in overall PM performance on the CAMPROMPT between LTHA ecstasy users and LTLA ecstasy, U=102.50, *p*=.15.

Study 2

8.4 Method

Participants

The participants in the present study were the same as those who participated in Study 1.[2] They were divided into 21 concurrent short-term high alcohol (STHA) ecstasy users (14 males), 21 concurrent short-term low alcohol (STLA) ecstasy users (14 males) and 44 non-ecstasy users (16 males) (for demographic variables, see Table 7.3). The gender composition differed significantly between the groups, $\chi^2(2, 86)=7.90$, $p=.02$. There were more females (n=28) than males (n=16) in the non-ecstasy users group. There were more males (n=14) than females (n=7) in the LTHA ecstasy user group. There were also more males (n=14) than females (n=7) in the LTLA ecstasy users group. The mean period of abstinence for STHA ecstasy users was 7.47 weeks, median=3.00 weeks; the mean period of abstinence for STLA ecstasy users was 81.25 weeks, median=25.00 weeks).

Materials

Materials are as per Study 1. Additionally, from the background drug use questionnaire, for the 12-month period prior to the test-session, participants estimated the typical dose that they ingested in a representative session for each month. As per Study 1, participants also estimated the number of units of alcohol that they typically consumed per session of drug use (concurrent alcohol use). Data relating to typical frequency (times per week) of use in the 12-month period prior to the test-session was also collected. This was done for all illicit drugs during the 12 months prior to the test-session. Long-term data relating to drug use was collected as in Study 1. Estimates of total use for each respective drug and their average frequency of use (times per week) during the previous 12 months were calculated.

Procedure

Procedural details were reported in Study 1.

[2] The total number of ecstasy users in Study 2 exceeded those in Study 1 as a result of missing data.

Design/Statistics

A median split was used to dichotomise short-term concurrent alcohol use. For each month in the 12 months prior to the test-session, the typical number of units of alcohol consumed in a single session whilst using ecstasy was recorded. The resulting figures were averaged across the 12-month period (months during which the drug was not used are coded as zero) to produce an average and thus create two user groups (STHA ecstasy users and STLA ecstasy users). The median split for short-term concurrent alcohol use was 1.94 units of alcohol per session of ecstasy use. Participants who, on average, consumed 1.94 units of alcohol or more per session of ecstasy use in the 12 months prior to the test-session were classified as STHA ecstasy users and those who consumed less than 1.94 units were classified as STLA ecstasy users. The high and low alcohol groups together with a non-ecstasy user group constituted the three levels of the between participant IV.

The background measures and indeed the underlying data were the same as were used in Study 1 as were the PM DVs. However, the group classifications were based on short-term concurrent alcohol use as indicated above. Alternative background drug use variables were used. These included total ecstasy, cannabis and cocaine consumption in the previous 12 months, average typical ecstasy, cannabis and cocaine dose per session in the previous 12 months, short-term concurrent alcohol and ecstasy use (the typical number of units of alcohol consumed per session of ecstasy use, averaged over the 12 months prior to the test-session) average frequency (times per week) of ecstasy, cannabis and cocaine use in the previous 12 months and total ecstasy, cannabis and cocaine consumption in the previous 30 days. In light of the distributional characteristics of the individual measures, and the tripartite nature of the IV, the same mix of parametric and non-parametric analyses were employed as in Study 1.

8.5 Results

Demographical and Background Variables

Demographic and background scores (age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression) are set out in Table 8.4. Various indices of short-term background drug use variables were compared between STHA ecstasy uses, STLA ecstasy users and non-ecstasy users. These data are shown in Table 8.5.

Table 8.4 Demographical variables of short-term high alcohol ecstasy users, short-term low alcohol ecstasy users and non-ecstasy users.

	STHA ecstasy users		STHA ecstasy users		Non-ecstasy users		p
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
Age (years)	21.33 (1.62)	21	23.43 (7.17)	21	20.09 (2.12)	44	.008**
Raven's Progressive Matrices (max 60)	44.60 (5.55)	20	45.71 (6.48)	17	44.45 (7.98)	42	.83
Years of education	15.86 (1.49)	21	15.23 (2.84)	20	14.55 (1.81)	42	.06
Alcohol (units per week)	21.16 (20.93)	19	12.41 (11.43)	18	9.96 (12.11)	42	.02*
Cigarettes per day	6.60 (3.67)	10	5.95 (4.52)	10	6.94 (2.93)	8	.86
Epworth Sleepiness Score	7.30 (2.74)	20	7.16 (3.91)	19	6.73 (3.07)	40	.76
Arousal	18.44 (5.61)	18	20.33 (3.45)	18	19.62 (3.380)	39	.40
Anxiety	12.11 (3.83)	18	11.56 (3.24)	18	11.26 (2.83)	38	.65
Depression	12.44 (2.81)	18	12.56 (3.20)	18	12.54 (2.49)	39	.99

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

One-way ANOVA showed that there was a significant difference between the STHA ecstasy users, STLA ecstasy users and non-ecstasy users in terms of age. Tukey's post hoc test showed that non-ecstasy users were significantly younger than STLA ecstasy users. There was no significant difference in age between non-ecstasy users and STHA ecstasy users or STHA ecstasy users and STLA ecstasy users.

One-way ANOVA showed that there was a significant difference between STHA ecstasy users, STLA ecstasy users and non-ecstasy users in terms of the typical number of units of alcohol that they consumed each week. Tukey's post-hoc test showed that, on average, STHA ecstasy users consumed more units of alcohol per week compared to non-ecstasy users. There was no difference in the typical number of units of alcohol consumed each week by non-ecstasy users and STLA ecstasy users or STHA users and STLA ecstasy users.

One-way ANOVAs revealed comparable group performance for intelligence (Raven's Progressive Matrices), years of education, cigarette consumption, Epworth Sleepiness Scale Score, arousal, anxiety, and depression (see Appendix 4 for detailed statistical analyses related to background variables).

Table 8.5 Background drug use variables of short-term high alcohol ecstasy users, short-term low alcohol ecstasy users and non-ecstasy users

	STHA ecstasy users					STLA ecstasy users					Non-ecstasy users					p
	Median	Min.	Max.	Int. Range	n	Median	Min.	Max.	Int. Range	n	Median	Min.	Max.	Int. Range	n	
Total use in the last 12 months																
Ecstasy (tablets)	10.00	.40	96.00	39.00	21	.00	.00	6.50	3.00	21	-	-	-	-	-	<.001***
Cannabis (joints)	5.00	.00	5760.00	288.00	12	6.00	.00	2520.00	71.25	17	53.05	.00	1008.00	120.00	19	.68
Cocaine (lines)	27.00	.00	452.00	114.75	20	.00	.00	59.50	5.50	17	15.50	1.00	30.00	-	2	<.01**
Average typical dose of drug over the previous 12 months																
Ecstasy	.79	.08	3.17	1.46	21	.00	.00	.54	.23	21	-	-	-	-	-	<.001***
Cannabis	.42	.00	20.00	3.00	19	.17	.00	7.50	1.94	17	.79	.00	3.04	2.69	12	.73
Cocaine	2.25	.00	10.21	5.32	20	.00	.00	2.75	.46	17	1.29	.08	2.50	-	2	.<.001***
Alcohol consumed concurrently with ecstasy (units per session) averaged over the previous 12 months	5.00	2.00	20.83	4.17	21	.57	.00	1.88	1.13	21						<.001***
Average frequency of use in the last 12 months (times per week)																
Ecstasy	.08	.00	.60	.17	21	.00	.00	.06	.04	21	-	-	-	-	-	<.001***
Cannabis	.08	.00	7.00	3.00	19	.06	.00	7.00	.73	17	.43	.00	6.00	.93	12	.62
Cocaine	.06	.00	.94	.21	20	.00	.00	.40	.02	17	.14	.02	.25	-	2	.<.001***
Total use in the last 30 days																
Ecstasy (tablets)	.00	.00	12.00	1.75	21	.00	.00	.50	.00	18	-	-	-	-	-	.03*
Cannabis (joints)	.50	.00	480.00	40.50	18	.75	.00	225.00	7.50	16	1.50	.00	180.00	38.75	8	.003**
Cocaine (lines)	.00	.00	22.50	10.00	19	.00	.00	22.50	.00	15	2.50	.00	5.00	-	2	..009**
Number of weeks since last use																
Ecstasy	3.00	.43	26.00	8.50	21	25.00	1.00	624.00	57.50	20	-	-	-	-	-	<.001***
Cannabis	1.00	.12	208.00	20.82	18	1.00	.00	520.00	11.56	17	2.50	.00	104.00	11.68	12	1.00
Cocaine	3.50	.00	108.00	12.18	18	20.00	3.00	780.00	99.00	16	3.00	2.00	4.00	-	2	.011*

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

Inferential statistics for those outcomes in Table 8.5 that were not significant are reported in Appendix 4. Similarly all other pairwise differences that are not explicitly referred to below are non-significant and the inferential statistics are presented in Appendix 4.

The data in Table 8.5 shows that compared to STLA ecstasy users, STHA ecstasy users consumed more ecstasy in the 12 months prior to the test-session and also consumed more ecstasy tablets per session during this period. Mann-Whitney U tests revealed that these differences were statistically significant, U=41.50, p<.001. U=33.50, p<.001, respectively. With regard to concurrent alcohol and ecstasy use and the manner in which the short-term concurrent alcohol ecstasy users were divided, the median data in Table 8.5 shows that relative to STLA ecstasy users, STHA ecstasy users typically consumed more units of alcohol per session of ecstasy use in the 12 months prior to the test-session. As expected, the group difference was significant U=.00, p<.001. STHA ecstasy users used ecstasy more frequently than STLA ecstasy users during the 12 months prior to the test-session with Mann-Whitney U test revealing that this trend was statistically significant, U=32.50, p<.001. In relation to period of abstinence, STHA ecstasy users had used ecstasy more recently than STLA ecstasy users. Mann-Whitney U test showed that the group difference was significant, U=75.50, p<.001. Table 8.5 shows that STHA ecstasy users consumed more ecstasy in the 30 days prior to the test-session than STLA ecstasy users. The group difference was significant, U=133.00, p=.03.

In relation to the group differences on short-term cannabis use measures, Table 8.5 (see Chapter 8) shows that non-ecstasy users had used more cannabis than both STHA ecstasy users and STLA ecstasy users in the 30 days prior to the test-session. By comparison, STHA ecstasy users and STLA ecstasy users had used a similar number of cannabis joint in the 30 days prior to the test-session. Kruskal-Wallis test showed that the group difference was significant, $\chi^2(2)=11.76$, p=.003. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) revealed that non-ecstasy users consumed significantly less cannabis in the previous 30 days compared to STHA ecstasy users, U=264.50, p=.002 and STLA ecstasy users, U=272.00, p=.003. There was no significant difference in the number of cannabis joints consumed in the last 30 days between STHA ecstasy users and STLA ecstasy uses, U=188.50, p=.73.

Given that there were only two non-ecstasy cocaine users, comparisons on the short-term cocaine use measures were restricted to the two short-term concurrent alcohol and ecstasy user groups. In the 12 months prior to the test-session, STHA ecstasy users consumed more cocaine, consumed higher doses of cocaine per session and used cocaine more frequently than STLA ecstasy users. The respective Mann-Whitney U tests revealed that all these differences reached significance (U=61.50, p<.001, U=61.50, p<.001,U=59.00, p<.001). STHA ecstasy users had also used more cocaine than STLA ecstasy users in the 30 days prior to the test-session, U=137.50, p=.0. In terms of period of abstinence, STHA ecstasy users had used cocaine more recently than STLA ecstasy users, U=64.50, p=.005.

Laboratory-based measures

Outcomes for the laboratory-based measures of PM for STHA ecstasy users, STLA ecstasy users and non-ecstasy users are summarised in Table 8.6.

Table 8.6 Mean, Standard Deviations (SD), Median, Minimum (Min.), Maximum (Max.) and Interquartile Range scores for short-term high alcohol ecstasy users, short-term low alcohol ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall task, the Karolinska fatigue PM task and the Cambridge PM test.

	STHA ecstasy users n=21					STLA ecstasy users n=20					Non-ecstasy users n=44					p
	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	
F1 event-based PM task																
Trial 1 errors	.55 (1.05)	.00	.00	3.00	.75	.60 (1.14)	.00	.00	3.00	.75	.14 (.65)	.00	.00	3.00	.00	.05*
Trial 2 errors	.15 (.67)	.00	.00	3.00	.00	.30 (.92)	.00	.00	3.00	.00	.00 (.00)	.00	.00	.00	.00	.14
Trial 3 errors	.00 (.00)	.00	.00	.00	.00	.35 (.22)	.00	.00	3.00	.00	.05 (.22)	.00	.00	1.00	.00	.03*
Total errors	.70 (1.53)	.00	.00	6.00	.75	1.25 (2.24)	.00	.00	8.00	2.00	.19 (.67)	.00	.00	3.00	.00	.04*
Long-term delayed recall PM task																
Total number of recall tests returned (max of 3)	.67(1.15)	.00	.00	3.00	1.50	.90 (1.17)	.00	.00	3.00	2.00	1.41 (1.42)	1.00	.00	3.00	3.00	.08
Karolinska fatigue PM task																
Percentage completed in first half of test-session	85.67 (15.67)	85.71	60.00	100.00	26.66	84.92 (14.94)	81.67	50.00	100.00	20.00	91.31 (16.00)	100.00	20.00	100.00	80.00	.10
Percentage completed in second half of test-session	36.06 (31.31)	33.33	.00	100.00	50.00	48.34 (32.81)	40.00	.00	100.00	50.78	79.92 (27.91)	100.00	.00	100.00	27.09	<.001***
Percentage completed overall	60.08 (20.56)	60.00	30.00	100.00	28.87	64.49 (22.48)	59.17	30.00	100.00	32.89	86.09 (17.53)	90.45	27.27	100.00	21.25	<.001***
Cambridge PM test																
Event-based PM performance	14.30 (4.01)	15.00	2.00	18.00	6.00	13.25 (3.78)	15.00	4.00	18.00	5.50	16.95 (1.97)	18.00	8.00	18.00	2.00	<.001***
Time-based PM performance	13.85 (4.01)	16.00	4.00	18.00	4.75	12.88 (3.42)	14.00	4.00	18.00	3.50	17.15 (1.97)	18.00	8.00	18.00	1.50	<.001***
Overall PM performance	28.15 (6.79)	29.00	12.00	36.00	8.75	26.13 (6.59)	28.00	8.00	36.00	6.00	34.15 (3.28)	36.00	20.00	36.00	2.00	<.001***

*p<.05, *p<.01***p<.001 *Note.* n for all groups was variable due to missing data. Twenty short-term high alcohol ecstasy users and 42 non-ecstasy users completed the F1 event-based PM task. Forty-two non-ecstasy users completed the Karolinska fatigue PM task. Twenty short-term high alcohol ecstasy users, 16 short-term low-alcohol ecstasy users and 40 non-ecstasy users completed the Cambridge PM test.

Examination of the data in Table 8.6 reveals that STHA ecstasy users and STLA ecstasy users made more errors than non-ecstasy users on trial 1 of the F1 event-based PM task while the two concurrent alcohol and ecstasy user groups performed similarly. There was a significant group difference in the number of errors that were made on trial 1 of the F1 event-based PM task, $\chi^2(2)=6.21$, $p=.045$. However, no significant differences were found between STHA ecstasy users and non-ecstasy users, U=338.00, $p=.03$, STLA ecstasy users and non-ecstasy users, U=337.00, $p=.02$ or STHA ecstasy users and STLA ecstasy users, U=198.00, $p=.97$. Nonetheless, in the first two cases the pairwise comparisons approached significance with nonusers making fewer errors.

The data in Table 8.6 reveals that STHA ecstasy users and STLA ecstasy users made more errors than non-ecstasy users on trial 2 of the F1 event-based PM task. STLA ecstasy users made more errors than STHA ecstasy users on trial 2 of the F1 event-based PM task. There was no significant difference between the groups in terms of errors that were made on trial 2 of the F1 event-based PM task, $\chi^2(2)=3.93$, $p=.14$

Table 8.6 reveals that STLA ecstasy users made more errors than both STHA ecstasy users and non-ecstasy users on trial 3 of the F1 event-based PM task. STHA ecstasy users and non-ecstasy users made a similar number of errors on trial 3 of the F1 event-based PM task. Contrary to expectation, STHA ecstasy users appear to have made no errors at all on trial 3 of the F1 event-based PM task. There was a significant group difference in the number of errors that were made on trial 3 of the F1 event-based PM task, $\chi^2(2)=6.86$, $p=.03$. However, none of the pairwise comparisons were significant: for STHA ecstasy users versus non-ecstasy users, U=400.00, $p=.33$,STLA ecstasy users versus non-ecstasy users, U=354.00, $p=.05$, and for STHA ecstasy users versus STLA ecstasy users, U=160.00, $p=.29$.

In terms of overall performance on the F1 event-based PM task, the data in Table 8.6 indicates that STHA ecstasy users and STLA ecstasy users made more errors than non-ecstasy users. STLA ecstasy users made more errors overall than STHA ecstasy users. The group difference in the number of errors made across all trails of the F1 event-based PM task was significant, $\chi^2(2)=6.65$, $p=.04$. STLA ecstasy users committed significantly more errors overall relative to non-ecstasy users, U=30.00, $p=.011$. There was no significant difference in the total errors committed on

the F1 event based PM task by STHA ecstasy users and non-ecstasy users, U=353.00, *p*=.10 or STHA ecstasy users and STLA ecstasy users, U=176.50, *p*=.53.

In terms of long-term time-based PM performance, inspection of the data in Table 8.6 shows that STHA ecstasy users returned a fewer number of delayed recall tests (The long-term delayed recall test) compared to STLA ecstasy users and non-ecstasy users. STLA ecstasy users remembered to return slightly fewer delayed recall tests than non-ecstasy users. One-way ANOVA revealed that the group difference in the number of delayed recall test sheets returned approached statistical significance, F(2,82)=2.64, *p*=.08, partial eta squared=.06. Helmert contrast revealed that the combined group of STHA ecstasy users and STLA ecstasy users returned significantly fewer delayed recall tests that non-ecstasy users, *p*=.03. A further Helmert contrast showed that there was no significant difference between STHA ecstasy users and STLA ecstasy users in terms of the number of delayed recall test that were returned, *p*=.57. Pairwise comparisons adjusted by Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that there was no significant difference between STHA ecstasy users (M=.67, SD=1.15) and non-ecstasy users (M=1.41, SD=1.42), *p*=.04 STLA ecstasy users (M=.90, SD=1.17) and non-ecstasy users, *p*=.15, or STHA ecstasy users and STLA ecstasy users, *p*=.41 in terms of the number of delayed recall tests that were returned on the long-term delayed recall task.

The data in Table 8.6 shows that compared to STHA ecstasy users and STLA ecstasy users, non-ecstasy users successfully completed a greater number of Karolinska fatigue questionnaires during the first and second halves of the test-session. Overall performance on the Karolinska fatigue questionnaire was better for non-ecstasy users compared to STHA ecstasy users and non-ecstasy users. STHA ecstasy users and STLA ecstasy users completed a similar proportion of Karolinska fatigue questionnaires during the first half of the test-session. However, compared to STHA ecstasy users, STLA ecstasy users remembered to complete more Karolinska fatigue questionnaires during the second half of the test-session. Overall performance on the Karolinska fatigue PM task was comparable between STHA ecstasy users and STLA ecstasy users.

There was no significant difference between the groups in terms of the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session, $\chi^2(2)=4.62$, $p=.099$. However, the difference did approach statistical significance. Post-hoc tests showed that that there was no significant difference in the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session by STHA ecstasy users and non-ecstasy users, U=342.00, $p=.09$, STLA ecstasy users and non-ecstasy users, U=380.00, $p=.06$ or STHA ecstasy users and STLA ecstasy users, U=203.00, $p=.85$.

One-way ANOVA showed that there was a significant difference between the groups in terms of the proportion of Karolinska fatigue questionnaires that were completed during the second half of the test-session, F(2,80)=17.41, $p<.001$, partial eta squared=.30. Helmert contrast showed that relative to non-ecstasy users, the combined group of STHA ecstasy users and STLA ecstasy users remembered to completed a significantly higher proportion of Karolinska fatigue questionnaires during the second half of the test-session, $p<.001$. However, a further Helmert contrast showed that there was no significant difference between STHA ecstasy users and STLA ecstasy users in terms of the proportion of Karolinska fatigue questionnaires that were completed during the second half of the test-session, $p=.19$. Pairwise comparisons adjusted by Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users (M=79.92, SD=27.91) remembered to complete a significantly higher proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to both STHA ecstasy users (M=36.03, SD=31.31), $p<.001$ and STLA ecstasy users (M=48.34, SD=32.81), $p<.001$. There was no significant difference in the proportion of Karolinska fatigue questionnaires that were completed during the second half of the test-session by STHA ecstasy users and STLA ecstasy users, $p=.19$.

One-way ANOVA revealed that there was a significant difference between STHA ecstasy users, STLA ecstasy users and non-ecstasy users in terms of overall performance on the Karolinska fatigue PM task, F(2,80)=15.67, $p<.001$, partial eta squared=.28. Helmert contrast showed that relative to non-ecstasy users, the combined group of STHA ecstasy users and STLA ecstasy users remembered to complete a significantly lower proportion of Karolinska fatigue questionnaires during the entire test-session, $p<.001$. However, a further Helmert contrast showed that there

was no significant difference between STHA ecstasy users and STLA ecstasy users in terms of the proportion of Karolinska fatigue questionnaires that were completed over during the entire test-session, p=.47. Pairwise comparisons adjusted by Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users (M=86.09, SD=17.53) remembered to complete a significantly higher proportion of Karolinska fatigue questionnaires during the entire test-session compared to both STHA ecstasy users (M=60.08, SD=20.56), p<.001 and STLA ecstasy users (M=64.49, SD=22.48), p<.001. There was no significant difference in the proportion of Karolinska fatigue questionnaires that were completed during the entire test-session by STHA ecstasy users and STLA ecstasy users, p=.47.

Examination of the data in Table 8.6 shows that non-ecstasy users successfully completed more event-based PM tasks on the CAMPROMPT compared to STHA ecstasy users and STLA ecstasy users. STHA ecstasy completed a similar number of event-based PM tasks on the CAMPROMPT compared to STLA ecstasy users. Kruskal-Wallis test showed that there was a significant group difference in terms of event-based PM performance on the CAMPROMPT, $\chi^2(2)=21.94$, p<.001. Non-ecstasy users were significantly better at completing event-based PM tasks on the CAMPROMPT than STHA ecstasy users, U=212.50, p<.001 and STLA ecstasy users, U=96.00, p<.001. No significant difference was found between STHA ecstasy users and STLA ecstasy users in terms of event based PM performance on the CAMPROMPT, U=127.50, p=.31.

Inspection of the data in Table 8.6 reveals that non-ecstasy users successfully completed more time-based PM tasks on the CAMPROMPT compared to STHA ecstasy users and STLA ecstasy users. STHA ecstasy users and STLA ecstasy users completed a similar number of time-based PM tasks on the CAMPROMPT. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of time-based PM performance on the CAMPROMPT, χ^2 (2)=31.61, p<.001. Non-ecstasy users completed a significantly higher number of time-based PM tasks on the CAMPROMPT than STHA ecstasy users, U=157.00, p<.001, and STLA ecstasy users, U=64.50, p<.001. No significant difference was found between STHA ecstasy users and STLA ecstasy users in terms of time based PM performance on the CAMPROMPT, U=121.50, p=.22.

In terms of overall PM performance on the CAMPROMPT, the data in Table 8.6 indicates that non-ecstasy users performed better than STHA ecstasy users and STLA ecstasy users. In addition, overall performance on the CAMPROMPT was comparable between STLA ecstasy users compared to STHA ecstasy users. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of overall PM performance on the CAMPROMPT, $\chi^2(2)=32.57$, $p<.001$. Overall PM performance on the CAMPROMPT was significantly higher for non-ecstasy users compared to STHA ecstasy users, U=131.00, $p<.001$, and STLA ecstasy users, U=60.50, $p<.001$. There was no significant difference in overall PM performance on the CAMPROMPT between STHA ecstasy users and STLA ecstasy, U=121.50, $p=.22$.

8.6 Discussion

A large proportion of drug users consume alcohol concurrently with ecstasy (Barrett et al., 2006; Grov et al., 2009; Fisk et al., 2009). This is problematic in light of evidence that suggests that the use either alcohol (Heffernan & Bartholomew, 2006; Heffernan et al., 2002; Heffernan et al., 2006) or ecstasy (Hadjiefthyvoulou et al., 2011a; 2011b) alone can be detrimental to PM performance. Moreover, the concurrent use of alcohol and ecstasy has been associated with cognitive impairments in memory and learning in animals (Hernandez-Rabaza et al., 2010; Vidal Infer et al., 2012). Further findings show that compared to the use of ecstasy alone, the concurrent consumption of alcohol and ecstasy can exacerbate abnormalities in PM-related neurotransmitters including dopamine (Vidal Infer et al., 2012). Thus, where apparent ecstasy-related deficits in PM have been observed, it is difficult to determine whether these effects are attributable to the use of ecstasy, alcohol or due to a combined effect of both drugs. The present research aimed to investigate the extent to which long- (use of the entire period of use, Study 1) and short-term (use over the last 12 months, Study 2) concurrent alcohol and ecstasy use can predict PM performance.

Clear ecstasy-related deficits in PM performance were observed in both studies. In Study 1, LTHA ecstasy users and LTLA ecstasy users remembered to complete significantly fewer Karolinska fatigue questionnaires during the second half of the test-session compared to non-ecstasy users. These differences remained statistically significant when completion rates were averaged over the first and second halves of the test-session. Non-ecstasy users also performed significantly better than LTHA ecstasy users and LTLA ecstasy users on the event- and time-based PM tasks of the CAMPROMPT. Similar findings were observed in Study 2 with both STHA ecstasy users and STLA ecstasy users remembering to complete significantly fewer Karolinska fatigue questionnaires during the second half of the test-session compared to non-ecstasy users. As per Study 1, non-ecstasy users also performed significantly better than STHA ecstasy users and STLA ecstasy users on the event- and time-based PM tasks of the CAMPROMPT. These findings coincide with a body of previous research that has found clear evidence of PM deficits in ecstasy users (Hadjiefthyvoulou et al., 2011a; 2011b, Rendell et al., 2007; Weinborn et al., 2011).

Although clear PM performance deficits were observed in each of the concurrent alcohol and ecstasy groups relative to non-ecstasy users, no significant PM performance differences were found between high dose concurrent alcohol and ecstasy users and low dose concurrent alcohol and ecstasy users. The overall findings from Study 1 showed that long-term concurrent alcohol and ecstasy use had no effect on any of the event- or time-based PM outcomes. This was demonstrated by LTHA ecstasy users and LTLA ecstasy users performing similarly on all laboratory-based measures of PM. Similarly, the findings from Study 2 showed that short-term concurrent alcohol and ecstasy use did not predict performance on any of the PM measures. Once again, STHA ecstasy users and STLA ecstasy users performed comparably on all laboratory-based measures of PM performance. These findings indicate that increased consumption of alcohol during a session of ecstasy use is not detrimental to PM performance. This result is inconsistent with animal research that has shown spatial and working memory deficits in rats following the concurrent administration of alcohol and ecstasy (Hernandez-Rabaza et al., 2010). Given the potential role of the central executive in PM tasks (Kopp & Thöne-Otto, 2000), concurrent alcohol and ecstasy-related effects were expected. However, this was not the case. One possible reason for the discrepancy in the findings might be linked to differences in the doses of alcohol and MDMA administered in Hernandez-Rabaza at al's (2010) study and the typical doses consumed by the concurrent alcohol and ecstasy users. Hernandez-Rabaza and co-workers (2010) note the possibility that the levels of alcohol and ecstasy which were administered to the rats in their study may not be representative of the typical doses consumed by humans. For instance, it might be that Hernandez-Rabaza and co-workers (2010) administered very high doses of alcohol and MDMA which are much larger than the doses typically consumed by humans thereby accounting for the cognitive impairments that were observed.

While concurrent alcohol and ecstasy use was not found to be related to PM performance, research surrounding this topic is still in its infancy and therefore warrants further investigation. To our knowledge, the empirical work presented in the current Chapter is the first of its kind to investigate the effects of concurrent alcohol and ecstasy use on PM performance. Thus, it is difficult to make explicit conclusions based only on the current findings. One possible explanation why no significant differences were found between the high dose concurrent alcohol and ecstasy user

groups and the low dose concurrent alcohol and ecstasy groups may be related to the way in participants were allocated to the groups. As stated previously, a median split was used to dichotomise ecstasy users with the number of units of alcohol consumed per session of ecstasy use being the primary factor for the split. In other words, ecstasy users were split into high and low alcohol concurrent alcohol and ecstasy users based solely on the number of units of alcohol consumed in a representative session of ecstasy use. Thus, it would be reasonable to assume that any differences observed between the resultant high and low concurrent alcohol and ecstasy user groups would be indicative of a performance deficit driven by increased alcohol consumption. An alternative approach would have been to divide the cohort of ecstasy use according to a product of their alcohol and ecstasy use together. However, had group differences been found, it would be unclear whether any effects were mediated by alcohol or ecstasy use. This is because high dose ecstasy users who consume relatively little alcohol in a representative session of ecstasy use would be classed in the same group as low dose ecstasy users who consume higher amounts of alcohol. Nonetheless, when this approach was adopted, findings were very similar to those found in the present study (see Appendix 5). Clear ecstasy-related impairments in PM were apparent while no detrimental effects of concurrent alcohol and ecstasy use were observed.

There are a number of limitations that must be considered in relation to the studies outlined in the current Chapter. One issue concerns the significant age difference that was found between the groups in both studies. In Study 1, non-ecstasy users were significantly younger than both LTHA ecstasy users and LTLA ecstasy users. In Study 2, non-ecstasy users were significantly younger than STLA ecstasy users. Having a significant age difference between the groups is problematic given that PM performance declines with age (Kvavilashvili et al., 2013). Since the concurrent alcohol and ecstasy user groups were significantly older than the non-ecstasy users in Study 1, it might be argued that PM differences are mediated by individual differences in age rather than ecstasy use. Nonetheless, further examination of the mean data in Tables 8.1 and 8.2 show that there were only small age differences between all groups. Concurrent alcohol and ecstasy user groups and non-ecstasy users in both studies were all in their early twenties. This is crucial given that PM performance does not appear to decline significantly until a person is in their 50’s

or 60's (Uttl, 2008). Thus, it is somewhat unlikely that the age-related group differences observed here give rise to PM differences in their own right.

The findings from Study 1 are further limited in that there was a significant difference between the groups in terms of the number of years of education. More specifically, non-ecstasy users had studied for a significantly shorter length of time compared to LTLA ecstasy users. Subsequently, non-ecstasy users may have been expected to demonstrate inferior PM performance compared to LTLA ecstasy users. However, the number of years of education may not be an accurate predictor of intelligence. Other more accurate indicators of intelligence were included as background variables including the Raven's Progressive Matrices task. Group comparisons on this measure of intelligence revealed that there was no significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users. With this in mind, one would not expect differences in the number of years of education between non-ecstasy users and LTLA ecstasy users to mediate PM differences.

Although ecstasy-related deficits in PM were observed, it is not possible to explicitly conclude that these impairments are attributable to ecstasy use alone. This is because a large number of the high and low concurrent alcohol and ecstasy users had in fact used other drugs including cannabis and cocaine. While it would have been desirable to include cannabis-only and cocaine-only control groups this was neither practical or realistic. First, the inclusion of a detailed and extensive test-battery meant that testing procedures totalled over two hours. Second, it is very difficult to obtain a sample of cannabis-only and cocaine-only users who do not use any other licit or illicit drugs. As stated earlier, the later empirical work in this thesis will use correlation analyses to control for cannabis and cocaine use with respect to PM deficits in ecstasy users.

To conclude, the present research failed to show a relationship between the concurrent use of alcohol and ecstasy and PM performance. However, this topic of investigation is yet to be thoroughly explored, especially in humans. However, clear ecstasy-related deficits in PM were observed and these findings support those from previous research. Later empirical work will use correlational analyses to further examine the extent of ecstasy-related PM deficits while controlling for the use of other illicit drugs.

Chapter 9: The role of executive functioning processes in prospective memory

Chapter Outline

This Chapter provides an introduction to the cognitive ability of executive functioning. Particular attention is placed on Miyake et al's (2000) theoretical model which proposes that executive functions or more specifically, the central executive can be fractionated into three separable processes: shifting, updating and inhibition. Common laboratory-based measures of executive functions are outlined and described. The extent to which updating, shifting and inhibition processes are impaired in ecstasy users is discussed. In line with this, the possibility that impairments in executive processes may impair prospective memory (PM) performance is examined.

9.1 What is Executive Functioning?

Executive functions are a set of general-purpose control mechanisms that control and regulate an individual's thoughts and behaviours. Executive functions are diverse in nature such that they include control functions related to inhibition of prepotent responses, shifting between mental sets, monitoring and regulating performance, updating task demands, maintaining goals, planning, working memory, and cognitive flexibility (Miyake & Friedman, 2012).

Executive functioning (EF) has been closely linked to working memory: the system responsible for active maintenance and manipulation of information over short time periods (Miyake & Shah, 1999). McCabe Roediger, McDaniel, Balota & Hambrick (2010) used a factor analytic approach to explore the extent to which these two cognitive constructs share a common underlying ability. McCabe and colleagues (2010) investigated the amount of variance which was common to each construct (EF and working memory) and the extent to which they were distinct from the general ability construct, processing speed (i.e., the speed at which people process information). Given that controlling for processing speed can account for a large amount of age-related variance in episodic memory (the information which relates to "what", "when" and "where" something happened; Kwok, Shallice & Macaluso, 2012), McCabe and colleagues (2010) also investigated whether EF and working memory account for unique age-related variance in episodic memory beyond that

accounted for by processing speed. EF, working memory, processing speed, episodic memory and general knowledge were assessed in a sample of younger adult (18-36 years), middle-age (36-55 years), younger-old (56-70 years) and older-old adults (71-90 years). The results showed a large correlation between EF and working memory (r=.97) whilst correlations between these constructs and processing speed were weaker (EF and processing speed, r=.78; working memory and processing speed, r=.78). The authors concluded that EF and working memory tasks measure a common attentional construct. They termed this construct, *executive attention*. This is because the EF and working memory tasks used to assess the respective constructs all required attentional ability (Banich, 2009; Braver, Gray & Burgess, 2007). Further, the term, executive attention, describes the functional nature of the construct. For example, executive attention is an attentional ability that is closely related to executive control functions. Further findings showed that, controlling for EF and working memory eliminated age effects on episodic memory. In addition, EF and working memory accounted for variance in episodic memory beyond that accounted for by processing speed. The overall findings confirm that EF and working memory share an underlying attentional ability and that this is strongly related to higher level cognition. This finding is particularly interesting given the assumed role of EF in PM ability (Kopp & Thöne-Otto, 2003; Heffernan & Bellis, 2012; Martin et al., 2003).

EF is multidimensional and as such there exists a number of different models and frameworks which provide different viewpoints as to its principal component processes (Banich, 2009). Some of the more influential models and in particular those models which will be applied later in this thesis are explored in the following paragraphs.

9.2 Theoretical models of executive functioning

An important construct in cognitive psychology which has been associated with the study of executive functions is Baddeley's (1986) multi-component model of working memory. Working memory refers to the system which is responsible for keeping things in mind while performing complex tasks such as reasoning, comprehension and learning (Baddeley, 2010). The concept of the multi-component model of working memory (Baddeley, 1986) is an extension of an earlier concept of short-term memory

(STM) that was proposed to comprise a unitary memory store (Atkinson & Shiffrin, 1968).

Atkinson and Shiffrin's (1968) multi-store model assumes that environmental stimuli receive attention from a sensory system (sensory memory) before being passed onto a limited capacity short-term memory (STM) store. The model proposes that information can only enter long-term memory (LTM) if it is maintained in STM for sufficient period of time. It is then recoded so that it can be stored in LTM. According to this model, the STM store acts as working memory in that it controls the flow of information into and out of LTM. Further to this, Atkinson and Shiffrin (1986) suggest that the STM/working memory system has a crucial role in learning and in wider cognitive tasks. However, the multi-store model is limited in that it cannot account for cases where patients with brain impairment show dysfunctions in STM but are able to form accurate long-term memories (Shallice & Warrington, 1970). According to Atkinson and Shiffrin's (1968) multi-store model, an impaired STM/working memory should lead to the rapid loss of information and as such the information should not be transferred to LTM. In addition, if the STM system does in fact act as a working memory system, then patients with impaired STM should demonstrate severe cognitive impairments. However, this is not the case and patients with dysfunctional STM are able to form accurate long-term memories and still live relatively normal lives (Baddeley, 2010; see Shallice & Warrington, 1970). In summary, Atkinson and Shiffrin's (1968) multi-store model fails in that it cannot explain the dissociation between STM and LTM.

The multi-component model of working memory (Baddeley, 1986; Baddeley, 1996) differs from the multi-store model (Atkinson & Shiffrin, 1968) in that it identifies a number of memory subsystems as opposed to a unitary module. In addition, the multi-component model emphasises the system's functional role in other cognitive tasks including learning, reasoning and comprehension.

The multi-component model proposes that a dedicated system is responsible for maintaining and storing information in the short-term and that this system mediates human thought processes (Baddeley, 2003). The model is based upon two "slave" systems which concern the processing of visuo-spatial sequences (the visuospatial sketchpad) and verbal sequences (the phonological loop). Each of the

“slave” systems are short-term storage systems which are allocated to their respective content domains (visuospatial or verbal sequences). The visuospatial sketchpad is limited in capacity (two or three objects) and is responsible for maintaining and manipulating visual images. Like its visual counterpart, the phonological loop is also limited in capacity (memory traces are held for two or three seconds before they fade) and is responsible for maintaining and manipulating acoustic information. A further component of Baddeley’s (1986) working memory model is the central executive which acts as a supervisory system (similar to the Supervisory Attentional System proposed by Norman & Shallice 1986) and is responsible for the control and regulation of cognitive processes (i.e., executive processes). Baddeley (2000) later added a further component to the multi-component model of working memory: the episodic buffer. The episodic buffer is another “slave” system which integrates units of visual, spatial and verbal information (language) and information from long-term memory into a unitary episodic representation (see Figure 1).

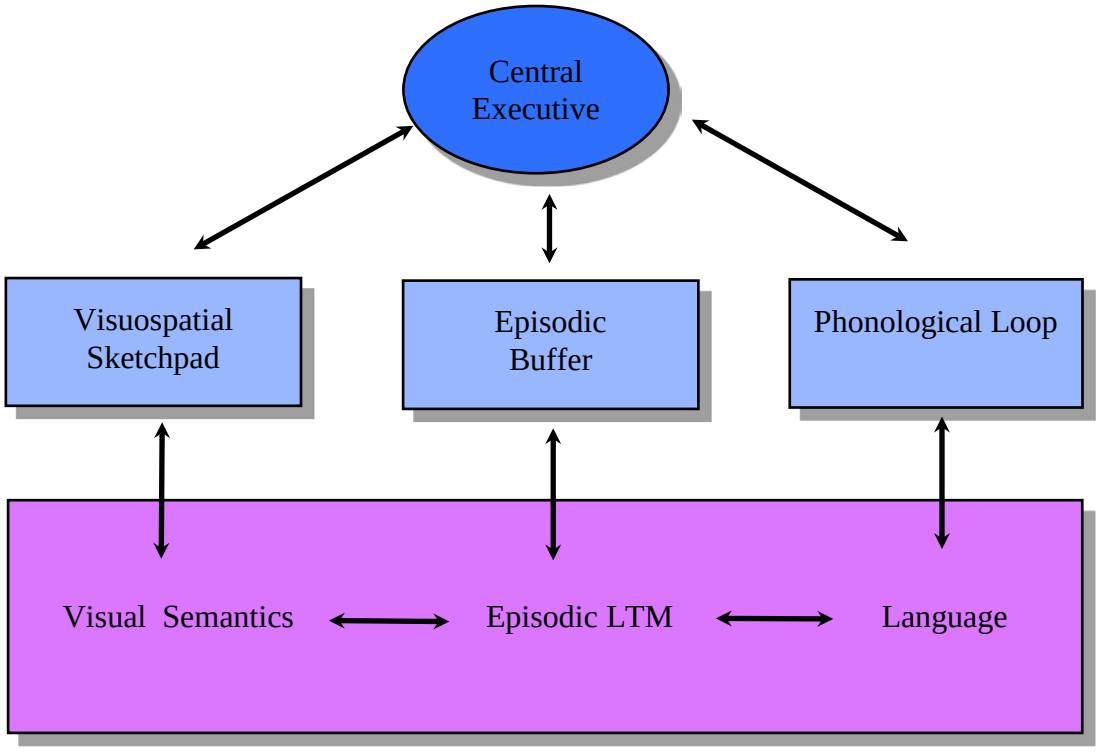

Figure 1. The latest revision of Baddeley's (1986; 2000) multi-component model of working memory.

While Baddeley's (1986; 2000) multi-component model of working memory suggests that there a number of subcomponents of memory which each control different aspects of human thought and behaviour, it does not identify any distinct subfunctions or subcomponents of the central executive. Rather, the multi-component model of working memory assumes that the central executive is unitary. However, there is substantial evidence for the nonunitary nature of executive functions. Evidence from clinical observation studies (Godefroy Cabaret, Petit-Chenal, Pruvo & Rousseaux, 1999; McKinlay, Grace, Dalrymple-Alford & Roger, 2010) and individual difference studies (Friedman et al., 2006; Friedman, Miyake, Robinson, & Hewitt, 2011; Miyake et al., 2000, Rose, Feldman, & Jankowski, 2011) have shown dissociations in performance on executive function tasks. For example, some patients may display impairment on some EF tasks but not on others suggesting that executive functions are distinctive and separable from each other (nonunitary).

A crucial individual difference study in the EF literature was conducted by Miyake et al. (2000). Miyake and colleagues (2000) argue that executive functions

and more specifically the central executive can be fractionated into three separable processes: updating, shifting and inhibition. Updating is closely linked to working memory (Lehto, 1996) and refers to the process whereby individuals monitor and code incoming information and revise stimuli already in working memory by replacing older, irrelevant information with newer, more relevant information (Morris & Jones, 1990). Aside from the simple maintenance of task-relevant information in working memory, updating involves the dynamic manipulation of the contents of working memory (Lehto, 1996; Morris & Jones, 1990). In other words, updating requires individuals to actively manipulate relevant information in working memory, instead of passively storing information. Shifting relates to an individual's ability to move back and forth between multiple tasks, operations or mental sets (Monsell, 2003). Shifting between mental sets is typically associated with a temporal cost (Rogers & Monsell, 1995). This might be because shifting requires an individual to disengage their attention from an irrelevant task whilst directing their attention towards a more relevant task. Alternatively, when an individual is required to perform a new operation on a set of stimuli, they might be faced with interference or negative priming after previously performing a different action on the same set of stimuli (Allport & Wylie, 2000). Inhibition refers to an individual's ability to inhibit dominant, automatic and prepotent responses (Stroop, 1935).

Miyake et al. (2000) used confirmatory factor analysis to examine the extent to which the three target executive functions are unitary. The authors chose a number of well-studied cognitive tasks which were hypothesised to investigate shifting (plus-minus task, adapted from Miyake et al., 2000; number-letter task, Rogers & Monsell, 1995; local global task), updating (keep track task, Yntema, 1963; the letter memory task, Morris & Jones, 1990; tone monitoring task) and inhibition (Stroop task, Stroop, 1935; antisaccade, Hallet, 1978; stop-signal task, Logan, 1994). In doing so, Miyake and colleagues (2000) were able to use latent variable analysis to determine the extent to which the three executive functions were unitary. A sample of 137 undergraduate students completed the nine EF tasks as well as five further tasks commonly used as measures of executive functioning.

Confirmatory factor analysis showed diversity amongst the three executive functions. Despite this, the shifting, updating and inhibition were not entirely independent from one another. A moderate correlation was found between the three

executive functions (shifting and updating, *r*=.56; shifting and inhibition, *r*=.42; updating and inhibition, *r*=.63) suggesting that the three executive functions tap some common underlying ability (unity). Taken together, the findings show both unity and diversity between shifting, updating and inhibition. This pattern of results has been replicated in other samples of twins (Friedman et al., 2011), pre adolescent children (Rose et al., 2011) and older adults (Vaughan & Giovanello, 2010).

Miyake and Friedman's (2012) unity/diversity framework attempts to identify the shared commonalities between the executive functions of shifting, updating and inhibition (unity) whilst distinguishing what is specific to each executive function (diversity). The "common executive function" identifies the unity aspect of the three executive functions and includes an individual's ability to actively maintain task goals and goal-related information. The "common executive function" also concerns how this information is used to effectively bias lower-level processing. According to Miyake and Friedman (2012), these abilities play a crucial role in all three executive functions.

In terms of diversity, shifting can be separated from the other executive functions (updating and inhibition) in that it requires flexibility. That is, shifting is dependent on an individual's ability to transition to new task-set representations. Less is understood about the unique features of updating compared to shifting and inhibition. However, it is suggested that updating requires effective channeling of information and controlled retrieval from LTM. The unity/diversity framework does not include an inhibition-specific component. This is because, the inhibition factor happens to correlate virtually perfectly with the "common executive function", leaving no inhibition-specific variance.

9.3 Assessment of Executive Functioning

9.3.1 Laboratory-based measures of Executive Functioning

Letter span task (Smith-Spark & Fisk, 2007)

The letter span test is a measure of working memory performance. Consonants are presented sequentially on a computer screen for 1.25 seconds. Participants are then required to recall the letters in the order in which they appeared. At first, participants are presented with three sets of two letters. The number of letters that participants have to recall is gradually increased to three, four and five letters until the individual fails on at least two of the three trials. Letter Span is scored according to the maximum number of consonants recalled in serial order.

The spatial span task (Smith-Spark & Fisk, 2007)

The spatial span task is a measure of visuospatial working memory performance. Participants are presented with a pattern consisting of a series of blank squares. The squares are then filled one at a time with X's. Participants are required to remember the position of each of the cells and to write down the positions of all the cells in the order in which they were filled. There are 12 positions in total which set out on the computer screen in a Corsi-type fashion. The number of positions which are filled with Xs is increased gradually over the course of the experiment. There were three trials at each level of the task. Participants only proceed to the next level if they successfully complete at least two of the three trials at the current level. Spatial span is defined as the maximum number of cells recalled in serial order as long as that level is achieved in at least two of the three trials for that particular level.

The random letter generation task (The RLG task; Baddeley, 1996)

The random letter generation task is a measure of inhibition performance. Participants are asked to recite letters in a random sequence whilst avoiding alphabetical and well-known letter sequences (e.g. ABC, BBC or TLC). Participants are also instructed to produce each letter with the same overall frequency. The task is commonly repeated three times whereby participants are asked to generate a total of 100 letters at a rate of one letter every 4 seconds, every 2 seconds or one per second. Results from the

random-letter generation task relate to a number of performance measures: 1) redundancy measures the extent to which each letter is produced with equal frequency; 2) alphabetical sequences measures the number of alphabetically ordered pairs which are repeated (e.g., AB, CD, WX, YX); 3) repeat sequences measures the number of pairs of letters which are repeated (e.g., AA, BB, XX, YY). In each case, a high score is indicative of poorer performance. The fourth performance measure refers to the total number of letters generated. In this case, a high score is indicative of good performance. Alphabetical and repeat sequences are suggested to load on the inhibition component of EF (Fisk & Sharp, 2004; Miyake et al., 2000). There is a degree of inconsistency in the literature as to whether or not the redundancy measure loads on any of the components of executive functioning. Some researchers propose that the redundancy measure is reflective of the updating component (Miyake et al., 2000) while others (Fisk & Sharp, 2004) do not.

The consonant updating task (see Montgomery, Fisk, Newcombe & Murphy, 2005b)
The consonant updating task is a measure of updating performance. The consonant updating task is a computer-based task where participants are presented with a sequence of random consonants based on their letter span score. A total of 24 lists are presented and, in each case, the participant is unaware of the number of consonants to be presented. The task is to recall the most recent *n* consonants in the order in which they appeared where *n* is equal to the participant's letter span score. Six trials are presented at four different list lengths and in a randomized order: *n*, *n* + 2, *n* +4 and *n* + 6 items. A composite score of updating performance is calculated based on the average number correct for each serial position over the six trials at each of the four list lengths. These figures are then averaged over list length and serial position.

The computation span task (see Fisk & Warr, 1996)
The computation span task is a measure of updating performance. Participants are required to solve simple arithmetic problems (e.g., 7+3=?) by circling one of three multiple-choice answers as each problem is presented. Participants are also required to recall the second digit of each presented problem (e.g., 3). Once all problems have been solved, participants are asked to write down the last digit from each computation in serial order. The computation span task begins with three trials with one arithmetic problem and increases by one problem to two, three etc. In order to proceed,

participants are required to successfully complete each aspect of the task in at least two of the three trials at the current level. Span is scored according to the maximum number of end digits recalled in serial order. Participants are also required to have solved the corresponding arithmetic problems correctly. The computation span task is suggested to load on the updating component executive processes (Fisk & Sharp, 2004).

The Chicago word fluency task (The CWFT; Thurstone & Thurstone, 1943)

The CWFT is a measure of an individual's ability to access long-term memory (Fisk & Sharp, 2004). Participants are given five-minutes to write down as many words as they can, beginning with the letter S. Once completed, participants are given a further four-minutes to write down as many four-letter words beginning with the letter C. Participants are instructed not to write any place names, people's name or plurals. Because plurals were not allowed, words such as " cats" and repetitions of words were excluded. Scores for each fluency task are the number of appropriate words generated in each case.

The digit span task (Subset of the Wechsler Adult Intelligence Scale 4th Version; Wechsler, 2008)

The digit span task is a measure of updating performance. In the digit span task (Forward version), participants are presented with a series of numbers on a computer screen and are asked to say each number out loud after it is presented. Participants are then required to write down each digit in the order that they appeared on the computer screen. The Digit Span Task (Forward version) commences with three trials with one number and increases by one number to two, three, four etc. Digit span is defined as the maximum number of digits that a participant can remember on two out of three trials.

The plus/minus task (Miyake et al., 2000)

The plus/minus task is a measure of shifting performance. The plus/minus task is adapted from Miyake et al. (2000) and consists of three lists of 30, two-digit numbers. For the first list, participants are asked to add 3 to each number and to write the

answer in a box situated to the right. For the second list, participants are required to subtract three from the two digit number. Finally, for a third list, participants are required to alternatively add and subtract three from each two digit number in the list. A stopwatch is used to record the total time it takes for participants to complete each list. A shifting cost of alternating between adding and subtracting is calculated as the difference between the time taken to complete list three and the average of the times taken to complete list one and list two.

The number/letter task (Adapted from Rogers & Monsell, 1995; Miyake et al., 2000). The number/letter task is a measure of shifting performance. In the number/letter task, participants are presented with a number/letter pair (e.g. D4) in one of four quadrants on a computer screen. If the target is in the top half of the screen, the task is to indicate if the letter is a vowel (A, E, I, O or U) or a consonant. If the target is in the bottom half of the screen, the task is to indicate if the number is odd or even. The practice version of the task comprises three sets. The target is presented in the top half of the screen for 12 trials, then the bottom half for 12 trials, and then in a clockwise rotation around all four quadrants for a further 12 trials. The main task follows the same structure, except there are 64 targets in each block. Therefore, the trials in the first two blocks require no switching, whereas the third set does. The shift cost is calculated based on the difference between the average reaction times of the third block and the averages of the first two blocks.

Trial Making Test-B (TMT-B; Reitan, 1992)
The TMT-B is a measue of shifting performance. The TMT-B requires participants to correct a sequence of numbers alternated with letters as quickly as possible (e.g., 1, A, 2, B, 3, C, 4, D, etc). The time taken to complete the task is the primary performance measure.

The Wisconsin Card Sorting Task (The WCST; Heaton, 1981)
The WCST is a measure of shifting performance. A deck of cards containing different numbers, different forms and in different colours are shown. The task is to sort the

cards according to one of three rules (i.e., numbers, forms or colours). Participants are unaware of the rules and must identify the sorting rules for themselves. After each sort, participants receive feedback in order to determine whether their sort was correct or not. Following successful completion of one full card sort (10 correct sorts in a row), the rule is changed and participants must shift their attention and sort the cards according to the new rule. Perseverative errors are calculated and reflect the extent to which the participants keep sorting cards according to a previously correct rule or to a rule that he or she was informed was incorrect in the preceding sort.

9.4 Neuropsychology of executive functioning

EF has primarily been linked to a number of frontal regions including the right orbitofrontal cortex, the dorsolateral prefrontal cortex, the cingulate gyrus and the basal ganglia amongst others (Rubia et al., 2009). However, executive function control is not limited to prefrontal areas with a growing body of research suggesting that posterior (mainly parietal) regions are also implicated in EF tasks. To name a few, the precuneus, the left inferior parietal cortex and the superior parietal cortex have all been linked to EF performance (Baker et al., 1996; Dagher, Owen, Boecker & Brooks, 1999; Hedden & Gabrieli, 2010). Overall, this evidence shows that EF is mediated by a diverse neural network that extends beyond anterior cerebral regions. The current subchapter focuses specifically on the neurological basis of executive functions in the context of Miyake et al's (2000) three component model of executive functioning.

Research which has employed neuroimaging techniques to explore cerebral activation during shifting tasks has found significant involvement of prefrontal, parietal and subcortical areas (Gurd et al., 2002; Hedden & Gabrieli, 2010). This general activation was confirmed in Wager, Jonides and Reading's (2004) metanalysis which concluded that seven separate brain regions are activated during shifting tasks. Importantly, the specific locations of activation appear to be divided between the anterior and posterior regions. For example, the dorsolateral prefrontal cortex (frontal) has been linked to the active maintenance of information in working memory (Cohen et al., 1997) while the inferior parietal lobule (posterior) is implicated when participants are required to shift their attention form one stimulus

response mapping to another (Badre & Wagner, 2006, Yeung, Nystrom, Aronson & Cohen, 2006). Other posterior regions which demonstrate activation during shifting tasks include the posterior parietal cortex and the superior parietal cortex (Sohn et al., 2001). Sohn and colleagues (2001) explain that these regions are important during goal-directed preparation for a subtask. Interestingly, coordinated activation is evident between the basal ganglia and prefrontal and parietal regions at rest and during shifting tasks (Cools, Ivry & D'Esposito, 2006). The basal ganglia has a functional role in shifting tasks and is reflected by poorer shifting performance following dopaminergic depletion, striatal lesions, and in Parkinson's disease patients (Cools, Rogers, Barker & Robbins, 2010, Monchi, Petrides, Mejia-Constain, & Strafella, 2007; Nagano-Saito et al., 2008).

A body of research has also explored the updating component of executive functions. The n-back task is one measure of updating whereby items (e.g., letters, spatial positions or non-verbal material) are sequentially presented and participants are required to decide whether the item is similar to the one presented *n* items previously. Performance on the n-back task has been linked to neural activation in the prefrontal dorsolateral cortex (BA 9/46), the inferior frontal cortex (BA 44), and the anterior cingulate, but also in cerebral posterior areas, such as the superior and posterior parietal cortex (BA 40/7) (Braver et al., 1997; Cohen et al., 1997; Jonides et al., 1997). Similarly, research that has used the random number generation task to investigate updating (Miyake et al., 2000) has also found significant activation of the dorsolateral prefrontal cortex and the inferior frontal cortex during task completion (Jahanshahi, Dirnberger, Fuller & Frith, 2000). More recent literature has linked the updating component of executive functions to the caudate (improved accuracy) and the ventrolateral prefrontal cortex (faster reaction times; Podell et al., 2012). Overall, the literature is consistent in demonstrating the importance of the prefrontal cortex in updating tasks (Montojo & Courtney, 2008; Roth, Serences & Courtney, 2006; Astle, Jackson & Swainson, 2008; Lenartowicz, Escobedo-Quiroz & Cohen, 2010). According to D'Ardenne et al. (2012), the brain updates context via a gating mechanism which is mediated by the prefrontal cortex. When the gating signal is present, inputs to the PFC are enhanced. This facilitates the activation (encoding) of new representation and replaces the ones previously maintained. The updated context information is then maintained until the next gating signal is present. Crucially,

D'Ardenne et al. (2012) propose that the gating signal occurs only when conditions have changed and when a new goal should be realised.

With regard to inhibition tasks, evidence from neuroimaging studies points towards the involvement of prefrontal, parietal and temporal areas (Chee et al., 2000; Collette et al., 2001; Collette et al., 2005; Garavan, Ross & Stein, 1999; Larrue, Celsis, Bès & Marc-Vergnes, 1994; Nelson et al., 2003). Specifically, the right inferior frontal gyrus has a functional role in resolving interference among potentially conflicting characteristics of a target stimulus (Nelson et al., 2003) while the left inferior frontal gyrus is activated when participants have to resolve interference in verbal working memory tasks (D'Esposito et al., 1999; Jonides, Smith, Marshuetz, Koeppe & Reuter-Lorenz, 1998). Other areas such as the anterior cingulate cortex are activated when participants are presented with conflicting stimulus-response associations (i.e., when an individual is required to inhibit a dominant, automatic and prepotent response; Nelson et al., 2003).

A large proportion of studies that have explored the cerebral mechanisms associated with inhibitory control have focused on patients with attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). This is because patients with both disorders display behavioural abnormalities relating to inhibitory control. ADHD is characterised by inattention, impulsiveness and hyperactivity, as well as neuropsychologcal (Rubia et al., 2007; Wilcutt et al., 2005) and fronto-striatal neurofunctional (Rubia et al., 2008, 2009; Smith et al., 2006) deficits in inhibitory functions (e.g., motor response inhibition, cognitive switching). By comparison, OCD patients exhibit poor inhibitory control towards unwanted obsessive, thoughts, behaviours and compulsions (Rubia et al., 2009). Neurological evidence indicates that ADHD patients consistently demonstrate underactivation of the bilateral inferior prefrontal cortex (Pliszka et al., 2006; Rubia et al., 2005, 2008; Smith et al., 2006], the ventrolateral and the dorsolateral inferior prefrontal cortex during inhibition tasks (Rubia et al., 2008, 2009). Similarly, OCD patients display structural (Huyser et al., 2009; Menzies et al., 2008) and functional abnormalities (Menzies et al., 2008; Woolley et al., 2008) within inhibitory control-related prefrontal regions. Thus, researchers have begun to postulate that inhibitory control deficits displayed in patients with ADHD and OCD might be related to deficits within

the fronto-striatal network (Huyser et al., 2009; Menzies et al., 2008). According to Rubia et al. (2009) the right orbitofrontal cortex, the left dorsolateral prefrontal cortex, the cingulate gyrus and the basal ganglia all play a part in inhibitory control. A number of these regions have also been associated with PM functioning (Okuda et al., 1998; 2007) and as such PM deficits might be underpinned by some impairment in inhibitory control.

As demonstrated above, the brain regions implicated in EF tasks are diverse and fractionated between the frontal and posterior regions. However, there is some degree of overlap between the brain regions implicated in shifting, updating and inhibition tasks. These findings further demonstrate the unity of executive functions. This assertion is supported by an influential study by Collette et al. (2005). The authors employed PET to investigate the neural networks associated with Miyake et al's (2000) three-component model of executive functioning. A global conjunction analysis revealed activation in the right intraparietal sulcus, the left superior parietal gyrus, and to a lesser extent, the left lateral prefrontal cortex common to shifting, updating and inhibition tasks. These areas appear to be general to all three EF tasks. Collette et al. (2005) concluded that the right intraparietal region is involved in selective attention to task relevant stimuli and also in the suppression of task irrelevant information. In comparison, the left superior region is linked to modal switching and integration processes while the activation of the lateral prefrontal cortex was evident in ongoing task functions related to the monitoring and temporal organisation of information. Activation of the right intraparietal sulcus, the left superior parietal gyrus and the lateral prefrontal cortex which are common to shifting, updating and inhibition tasks confirms previous proposals of the unity of executive functions (Miyake et al., 2000; Miyake & Friedman, 2012).

Other findings from Collette and co-workers (2005) provide significant evidence for the diversity of executive functions. Interaction analyses showed that the right supramarginal gyrus, left precuneus, left superior parietal cortex, right intraparietal sulcus and left middle and inferior frontal gyri were activated during shifting task completion. Activation of the frontopolar (BA10), superior (BA 6), middle (BA 9/46), inferior (BA 44/45) and orbitofrontal (BA 11) cortices were observed in updating tasks. Increased activation of the BA 10 confirms previous

findings (Van der Linden et al., 1999) and is particularly noteworthy given the role of the frontopolar cortex in PM tasks (Burgess et al., 2001; Okuda et al., 2007; Burgess, Scott & Frith, 2003; Simons et al., 2006). Thus, it is feasible that deficits in PM may occur as a result of a secondary impairment in updating ability. Although Collette et al. (2005) found widespread prefrontal activation during updating tasks, the specific locations were different to the regions which were activated during shifting tasks. In terms of inhibition, significant activation was found in the right inferior frontal gyrus (BA 48), right orbitofrontal gyrus (BA 11) and the right middle/superior frontal gyrus (BA 10). It is important to note the area of the BA10 that was activated during inhibition tasks was different to the location that was activated during updating tasks. Furthermore, the authors are clear in demonstrating the more important function of the BA 10 for updating relative to inhibition (Collette et al., 2005).

In summary, shifting, updating and inhibition appear to be mediated by frontal networks whereby each executive function has been shown to map onto the left middle and inferior frontal gyri (Collette et al., 2005). However, each executive function as outlined by Miyake et al. (2000) (shifting, updating and inhibition) also appear to activate distinct and separate neural networks divided between the anterior and posterior regions. In the context of the current thesis, it is interesting to note that a number of the brain regions which have been linked to EF tasks are also implicated during PM tasks. For instance, activation of the left superior region (Collette et al., 2005) and the lateral prefrontal cortex (Collette et al., 2005; Rubia et al., 2009) which are suggested to be implicated in EF tasks have also been associated with PM performance (Burgess et al., 2001; Okuda et al., 1998; Okuda et al., 2007). Thus, it is plausible that ecstasy-related deficits in EF may give rise to substantially worse performance on PM tasks.

9.5 Executive functioning deficits in ecstasy users

The use of ecstasy has been linked to an array of cognitive deficits including in executive functions. The paragraphs that follow will focus primarily on the research that has explored the effects of ecstasy use on executive processes in the context of Miyake et al. (2000) conceptual framework of EF. The extent to which ecstasy has been shown to affects updating, shifting and inhibition will be examined.

Updating

According to Morris and Jones (1999), updating is a process that requires individuals to monitor and code information whist simultaneously revising stimuli already in WM. In other words, updating involves the replacement of older irrelevant information with newer and more relevant information. To do this, individuals must dynamically manipulate information stored in WM.

Updating executive processes have been examined in ecstasy users using a number of laboratory-based measures including the computation span task, the consonant updating task, the letter span task and the spatial span task. In one study, Montgomery et al. (2005b) used the computation span task and the consonant updating task to assess updating performance in 27 ecstasy users and 34 non-ecstasy users. Clear ecstasy-related deficits were observed on both measures indicating that the use of ecstasy may be detrimental to updating executive performance. These findings were replicated in another study by Montgomery and Fisk (2008). Seventy-three ecstasy/polydrug users and 73 non-ecstasy users completed the letter span task, spatial span task and the consonant updating task. Both spatial and consonant updating performance were significantly poorer in ecstasy/poldrug users relative to non-ecstasy users. In explaining their findings, the authors suggest that ecstasy users have problems with the active maintenance of information in WM. For example, while ecstasy/polydrug users might be able to form memory "chunks" of stimuli (numbers or letters), they may not be able to retain this information as effectively as non-ecstasy users. In a further study, the same authors (Fisk & Montgomery, 2009) sought to explore whether ecstasy-related deficits in updating executive processes are domain specific. That is, does ecstasy use adversely affect both verbal and visuo-spatial processing. Fourteen heavy ecstasy users, 39 light ecstasy users and 28 non-ecstasy users were assessed on the letter span task, the spatial span task and the computation span task. Ecstasy-related impairments were found on both the spatial span task and the computation span task such that non-ecstasy users performed significantly better than the combined group of heavy and light ecstasy users. These findings remained statistically significant after controlling for the effects of other illicit drugs. In summary, these findings suggest that updating executive deficits in

ecstasy users are in fact domain general with impairments being observed in both spatial and verbal domains.

In conclusion, the research discussed above suggests that updating performance is significantly impaired by the use of ecstasy. This is a view that was put forward in Murphy, Wareing, Fisk and Montgomery's (2009) review. Based on a review of 33 studies investigating the effects of ecstasy use on EF, Murphy and co-workers (2009) concluded that ecstasy-related deficits were particularly apparent in cognitive tasks that involved the updating of verbal material and for visuo-spatial tasks requiring additional processing beyond storage and retention. A more recent meta-analysis by Murphy et al. (2012) showed that ecstasy users were particularly impaired on visuo-spatial updating tasks that involve detailed processing including the recall of spatial stimulus elements, the recognition of figures and/or the production or reproduction of figures.

Shifting

Being able to move back and forth between multiple tasks, operations or mental sets is necessary for everyday functioning. This process is known as shifting and is often associated with a temporal cost (Monsell, 2003; Rogers & Monsell, 1995) resulting from interference and/or negative priming (Allport & Wylie, 2000). Some of the most common laboratory-based tasks that are used to assess shifting include the TMT-B, the WCST, the plus/minus task and the number/letter task.

Studies that have used the TMT-B have failed to highlight ecstasy-related impairments in shifting (Semple et al., 1999; Morgan, McFie, Fleetwood & Robinson, 2002; Thomasius et al., 2003). Morgan et al. (2002) found that there was no significant difference between current ecstasy users, former ecstasy users, polydrug controls and non-ecstasy users on the TMT-B. This finding was replicated by Thomasius et al. (2003) who found that current heavy ecstasy users, former ecstasy users, polydrug controls and non-ecstasy users took a similar length of time to complete the TMT-B.

No clear ecstasy-related deficits in shifting have been observed in studies that have used the WCST. For example, Turner, Godolphin and Parrott (1999) found that

ecstasy users were unimpaired compared to non-ecstasy users on the WCST. Similarly, Fox, Parrott and Turner (2001) found that there was no difference in perseverative errors on the WCST between 20 ecstasy users (with self-reported ecstasy-related problems), 20 non-problematic ecstasy users and non-ecstasy users. Thomasius et al. (2003) showed that current ecstasy users committed significantly more perseverative errors than polydrug users on the WCST, although their performance was not significantly different from that of non-ecstasy users. More recent research by McCann, Peterson and Ricaurte (2007) also failed to show shifting deficits in ecstasy users on the WCST.

The plus/minus task and the number/letter task have only been used in one study to date to investigate shifting performance in ecstasy users. Montgomery et al. (2005) found no significant differences in shift cost on the plus/minus task or the number/letter task between ecstasy/polydrug users and non-ecstasy users. The findings from this study as well as those documented above (Morgan et al., 2002; Thomasius et al., 2003) would appear to indicate that shifting performance is unaffected by the use of ecstasy. However, ecstasy-related impairments in shifting have been noted elsewhere (Dafters, 2006).

Dafters (2006) compared inhibition and shifting performance in ecstasy and cannabis users, cannabis-only users and non-ecstasy users using a standard version of the Stroop task (Stroop, 1935) and a modified alternative. The standard version of the Stroop task is suggested to load on the inhibition executive component and requires participants report the colour of the ink in which a word is printed while ignoring an incompatible word name. For example, the word blue written in yellow ink would require a response of yellow. Response times are typically slower for incompatible trials (when the colour of the ink and the word are different) compared to compatible trials (when the colour of the ink and the word are the same). The modified version of the Stroop task included in Dafters' (2006) study introduced a simple shifting EF element to the task. When a word was marked with a stimulus, for example, if a word was underlined, participants were required to identify the name of the word rather than the colour of the ink. No significant group differences were observed on the normal version of the Stroop task (inhibition). However, the ecstasy and cannabis user group were significantly impaired on the modified version of the Stroop task (shifting) relative to cannabis-only users and non-ecstasy users. Overall, these

findings appear to show an impairment in shifting executive processes associated with ecstasy use. However, as discussed earlier, there is a substantial amount of literature that suggests that the use of ecstasy is not detrimental to shifting. This is a point that is highlighted in Murphy et al's (2009) critical review of 33 published studies investigating EF in the context of Miyake et al's (2000) conceptual framework (i.e., studies investigating the effects of ecstasy use on updating, shifting and/or inhibition). The authors concluded that the shifting component of EF is relatively unaffected by ecstasy use.

Inhibition

The ability to inhibit dominant, automatic and prepotent responses is known as inhibition (Stroop, 1935). The Stroop task (Stroop, 1935) is a common measure of inhibition that is widely used in the literature. Studies that have used the Stroop task have shown no clear effects of ecstasy use on inhibition (Croft, Mackay, Mills and Gruzelier, 2001; Dafters, 2006; Morgan et al., 2002). Dafters (2006) found no significant difference in response times on the Stroop task between ecstasy and cannabis users, cannabis only users and non-drug users. Yip and Lee (2005) did claim to find evidence of ecstasy-related impairments on the Stroop task although their ecstasy user group (i.e., ecstasy users who did not use alcohol or tobacco) was unrepresentative of typical ecstasy users. It is common for drug users to typically consume ecstasy together with other drugs including alcohol and tobacco (either concurrently or at different times). For example, Riley and co-workers (2001) found that 85% of those individuals who consume ecstasy at rave events also use alcohol concurrently.

The Tower of London (TOL) task is another laboratory-based measure that is commonly used in the literature to assess inhibition. In this task, participants use an abacus to move three coloured balls (blue, red and green) from a starting position to a 'goal' position in a specified minimal number of moves. A total of 12 trials are completed involving two 2-move trials, two 3-move trials, four 4-move trials and four 5-move trials. Trials are tape-recorded and 'planning times' and 'solution times' are then calculated. Planning time reflects the interval from the last verbal instruction from the experimenter to the first 'click' of the apparatus from the participant.

Solution time reflects the total period of time that it takes the participant to complete a problem. Planning and solution times are averaged across the total 12 trials. Mean total number of errors made and total number of trials completed are also scored. Studies that have used the TOL task to investigate inhibition executive processes in ecstasy users have yielded inconsistent findings. Morgan (1998) found no difference between ecstasy users, polydrug controls and non-drug users on any of the performance measures of the TOL. Similar findings have been reported elsewhere with the majority of research failing to find ecstasy-related deficits in inhibition processes using the TOL task (Fox et al., 2001; Fox et al., 2002). Although the ecstasy user groups (problem ecstasy users and non-problem ecstasy users) in Fox et al's (2001) study did display significantly longer planning times than non-ecstasy users, no performance deficits were observed.

Previous literature has also failed to identify ecstasy-related problems in inhibition on the RLG task (Fisk & Montgomery, 2009; Fisk et al., 2004). For example, Fisk et al. (2004) found that current ecstasy users and non-ecstasy users generated a similar number of alphabetical sequences and repeat sequences on the one-second, two-second and four-second trials of the RLG task. These findings were replicated in a subsequent study by Fisk and Montgomery (2009). Overall, the general consensus in the literature appears to be that the inhibition component of EFs are unaffected by ecstasy use. This position is maintained in Murphy et al's (2009) critical review (also see Parrott, 2013).

In summary, updating executive processes are clearly impaired in ecstasy users with significant deficits having been observed in studies using the computation span task and the consonant updating tasks. This does not appear to be the case for shifting or inhibition executive processes where conclusive ecstasy-related deficits have not been found.

9.6 Are drug-related deficits in prospective memory underpinned by executive functioning processes?

Kopp and Thöne-Otto (2003) suggest that central executive functions play an important role in PM performance. One proposal is that PM performance is dependent

on the frontal regions and the functions that this region serves in mediating executive processes (Burgess, Veitch, de Lacy Costello & Shallice, 2000; McDaniel, Glisky, Rubin, Guynn & Routhieaux, 1999). For instance, frontally mediated executive functions include planning, interruption and inhibition processes, the monitoring of environmental events and the flexible initiation of responses towards those events (Shimamura, Janowsky & Squire, 1991). As discussed previously, PM is a detailed process which involves four main phases including intention formation, intention retention, the retrieval of an intention and the execution of an intention (Ellis, 1996; Kvavilashvili & Ellis, 1996). Frontal regions are specifically suggested to be implicated during the intention formation and intention execution phases of PM tasks. It is therefore assumed that executive resources will be significantly challenged in PM tasks where there is increased emphasis on intention formation and intention execution (Martin et al., 2003).

By way of investigating this proposal, Martin et al. (2003) assessed PM performance in a sample of 80 adults using four different laboratory-based PM tasks. Each task placed different demands on each of the four phases of PM and as such were assumed to differentially challenge frontal/executive functions. The multitask PM paradigm (Kliegel et al., 2000) was selected which placed significant emphasis on the intention planning and execution phases of PM tasks. This paradigm is based on the six-element task developed by Shallice and Burgess (1991) and consists of three phases; an introduction phase, a delay phase and a performance phase. In the introduction phase, participants are required to develop a plan for executing a six-element PM task. Participants are instructed that they will have a total of six-minutes to complete all PM subtasks. The delay phase is the period of time prior to the six-minutes allocated for the PM tasks where individual difference variables can be assessed. The performance phase refers to the period of time in which the multitask PM paradigm had to be executed.

The second laboratory-based measure was an event-based PM task that involved the presentation of a specific PM target during an ongoing task. Participants were asked to make a predefined response whenever the PM target was presented. This task was based on a paradigm that was first introduced by Einstein et al. (1997)

and placed strong emphasis on the execution phase of the PM task. The third laboratory-based PM measure was a time-based PM task where participants were required to make a predefined response after a specific time period had elapsed. Once again, this task emphasized the execution phase of the PM performance. Participants were given the opportunity to monitor time by pressing the "yellow" key on a computer keyboard. After pressing this key, a counter clock would appear on the computer screen for a period of two seconds. Executive functions were analysed using the WCST (Heaton, 1981), the Stroop task (Stroop, 1935) and the TOL task (see Shallice, 1982).

Age related-declines in PM performance were observed on all of the laboratory-based PM tasks except on the Belonging subset of the RBMT. Executive functions predicted PM performance for complex PM paradigms and especially those with increased emphasis on the intention formation and intention execution. Furthermore, it is worthy of note that age-related differences in PM performance were dependent on age-related individual differences in frontal/executive functions. This is significant in terms of the current project since illicit drug users display similar EF impairments to older adults. For example, older adults (Herman, Mirelman, Giladi & Schweiger, 2010; Prakash et al., 2009) and illicit-drug users (Gouzoulis-Mayfrank et al., 2000; Gouzoulis-Mayfrank & Daumann, 2009; Zakzanis, Campbell & Jovanovski, 2007) display impairment on executive functions associated with frontal lobe functioning. With this in mind, it might be that PM deficits in ecstasy users are underpinned by problems in executive functions.

Wang, Cao, Cui, Shum and Chan (2013) used event-related potentials to investigate the neural correlates of PM and to explore whether working memory is implicated in prospective remembering. Participants completed a simple PM task and a number/letter span task and electrophysiological data were recorded. Participants with long working memory spans had shorter reaction times (during an ongoing task and towards PM cues) and also demonstrated smaller amplitudes in prospective positivity compared to participants with short working memory spans. PM retrieval is dependent on cognitive resources such that participants with a short working memory span need to make a greater effort to retrieve a PM intention from memory (as demonstrated by a greater amplitude of prospective positivity relative to participants

with a longer working memory span). These results suggest that working memory resources are implicated in the intention retrieval process of prospective remembering.

Studies that have explicitly investigated the role of executive functions in PM deficits among drug users have yielded inconsistent findings. Heffernan and Bellis (2012) investigated the role of the central executive (an important component of Baddeley's (1986) working memory model and refers to a set of processes that control the organisation and flow of information in memory) on laboratory-based PM performance in a sample of ecstasy users and non-ecstasy users. PM performance was measured by the CAMPROMPT and EF was measured using the reverse digit span task. The results confirmed previous findings (Hadjiefthyvoulou et al., 2011b) and showed significant ecstasy-related impairment on the CAMPROMPT. However, in contrast to Hadjiefthyvoulou et al. (2011b), Heffernan and Bellis (2012) found that the significant main effect of ecstasy use on PM dropped to below statistical significance after controlling for EF scores (i.e., central executive scores). This finding suggests that problems with central EF might be at the core of PM impairments in ecstasy users. Further findings from Weinborn et al. (2011) further demonstrate the link between executive functions and PM performance in ecstasy users. They found that ecstasy users were significantly impaired on PM tasks with longer delay intervals. Moreover, this deficit was associated with risky decision-making, deficits in target monitoring and failure to maintain cue interaction pairings. In summary of the abovementioned findings, it appears that executive functions are implicated in PM tasks thereby raising the possibility that ecstasy-related impairments in PM are mediated by underlying problems in EF.

That said, a number of studies have shown that PM deficits in ecstasy users are not underpinned by executive functions (Hadjiefthyvoulou et al., 2011a; 2011b; 2011c). In Hadjiefthyvoulou and colleagues' (2011c) study, 73 ecstasy/polydrug users and 67 polydrug/non-ecstasy users were assessed on executive functions and PM measures. The BRIEF-A is a self-report measure of executive functions and was used to identify possible behavioral manifestations of executive function in ecstasy/polydrug users in comparison to a non-ecstasy user control group. Three further laboratory measures of PM were administered including the long-term delayed recall PM task (Hadjiefthyvoulou et al., 2011a), the Karolinska fatigue PM task

(Hadjiefthyvoulou et al., 2011a) and the F1 event-based PM task (Hadjiefthyvoulou et al., 2011a). Ecstasy/polydrug users performed worse than the control group on seven out of the nine scales of the BRIEF-A (inhibit, self-monitor, initiate, working memory, plan and organization, task monitor and organization of materials). Ecstasy/polydrug users also displayed significant deficits on all three laboratory measures of PM compared to the control group. However, additional analyses revealed that the ecstasy-related deficits in PM were not mediated by the deficits observed on the executive function measure. While the authors acknowledge the importance of executive functions for PM functioning, they argued that observed deficits in these cognitive processes do not share a common basis.

9.7 Chapter summary

Executive functions regulate a person's thoughts and behaviours and include control functions that inhibit prepotent responses, update task demands, shift between mental sets, monitor performance and/or cues and maintain goals (Miyake & Friedman, 2012). In relation to Miyake et al's (2000) conceptualization of executive functions, ecstasy users appear to be impaired on measures of updating but relatively unimpaired on shifting and inhibition tasks. It is important to note that PM tasks load heavily on prefrontal regions that have an important role in executive function processing. There is at least some evidence for the role of executive functioning processes in PM tasks with some studies (Heffernan & Bellis, 2012) suggesting that PM deficits in ecstasy users might be mediated by underlying problems in executive functions. Nonetheless, this relationship has received little attention in the literature and additions studies are needed to further establish the relationship.

Chapter 10: The role of executive functioning deficits in accounting for prospective memory impairments in ecstasy users.

Chapter 10 investigates Prospective Memory (PM) and Executive Functioning (EF) performance (Updating, shifting, inhibition, verbal word fluency) in ecstasy users and non-users. Ecstasy users and non-users were compared on a range of PM (The F1 event-based PM task, the Karolinska fatigue PM task, the long-term delayed recall PM task and the Cambridge PM task) and EF measures (The computation span task, the plus/minus task, the number/letter task, the random letter generation task and the Chicago word fluency task). Stepwise multiple regression was then performed to investigate the extent to which PM deficits in ecstasy users were attributable to individual differences in updating (The computation span task), shifting (The plus/minus task, the number/letter task), inhibition (The random letter generation task) and verbal word fluency (The Chicago word fluency task).

10.1 Introduction

Prospective memory (PM) refers to an individual's ability to carry out intended actions and/or behaviours at some point in the future. As discussed in Chapter 2, PM is a detailed process that involves the formation of an intention, its retention in memory, its subsequent retrieval from memory and the execution of an action directed towards the fulfilment of that intention (Ellis, 1996). With regard to retrieval, intentions may need to be carried out a short- or a long-term after they have been initially formed (Ellis & Kvavilashvili, 2000). This is often where PM lapses occur as a person may need to interrupt ongoing everyday activities in order to successfully fulfil a delayed intention. Therefore, in PM tasks there is no specific reminder for an individual to search memory for a previously formed intention. As such, PM retrieval is entirely dependent of on an individual's ability to inhibit currently ongoing operations and to divert attention towards the retrieval of the intention from memory. PM deficits in ecstasy users have been observed by a number of studies (Hadjiefthyvoulou et al 2011a; 2011b; Rendell et al., 2007; Rendell et al., 2009; Weinborn et al., 2011) as well as in the earlier empirical work of this thesis.

The purpose of the present study was to determine whether PM performance in ecstasy users is mediated by performance on EF tasks. The context for the present investigation is Baddeley's (1986) multi-component model of WM. The multi-component model of WM suggests that there is a distinct system that is responsible for the maintenance and storage of information in the short-term and that this system mediates an individual's thoughts and behaviours. As discussed in Chapter 9, the multi-component model of WM consists of a phonological loop system, a visuo-spatial system and a modality free central executive. The phonological loop and visuo-spatial system are responsible for the maintenance of acoustic and visual information, respectively. By comparison, the central executive is a supervisory system that controls and regulates cognitive operations. Research now indicates that the central executive can be separated into individual and partially independent components which load onto at least three different executive processes (Friedman et al., 2010; McKinlay et al., 2010; Miyake et al., 2010). Miyake and co-workers (2000) propose that the central executive can be sub-divided into three separate processes: shifting, updating and inhibition.

Shifting relates to an individual's ability to move back and forth between different tasks, operations and mental sets and is commonly associated with a temporal cost (Monsell, 2003; Rogers & Monsell, 1995). Updating involves monitoring and coding of incoming information such that individuals are required to revise stimuli already in WM and replace older, no longer relevant information with newer, more relevant information (Allport & Wylie, 1999). Inhibition refers to an individual's ability to inhibit dominant, automatic and pre-potent responses at times when they are not needed or are inappropriate. Although Miyake and colleagues (2000) found that the three processes shared common characteristics, their findings were also indicative that the processes were separate with some EF tasks loading on just one or two specific executive processes. For example the Wisconsin card sorting task (WCST) was strongly related to shifting while the Tower of Hanoi task (TOH) was closely linked to inhibition. The random letter generation (RLG) task tapped into inhibition and updating but not shifting (see Miyake et al., 2000). Other laboratory-based tasks of EF including the computation span task are associated most strongly with updating (Fisk & Sharp, 2004) while the plus/minus task and the number-letter task both load heavily on shifting operations (Montgomery et al., 2005b).

There is a growing body of evidence which links PM performance to executive functioning (EF) processes. This research is based on the assumption that PM requires self-initiated and attention demanding resources which load heavily on EF operations and frontal brain regions (Burgess et al., 2000; Marsh & Hicks, 1998). This theory is supported by findings that have shown that EF processes are predictive of performance on complex PM paradigms (Martin et al., 2003). Kliegel, McDaniel and Einstein (2000) used the six-element task (Shallice & Burgess, 1991) and found further evidence for the role of EF processes in PM performance. As discussed previously, the six-element task requires individuals to self-initiate six different subtasks during a limited time period. Each subtask needs to be scheduled and prioritized in the order in which the participant feels will allow them to complete as many of the PM tasks as possible during the time period. To measure active planning processes, participants are asked to generate a plan prior to the execution of the PM tasks. Kliegel et al. (2000) found that individuals with greater WM capacity were more likely to execute previously formed intentions on the six-element task. Successful performance on PM tasks required participants to reinstate intentions into WM. Inhibition was significantly related to the number of individual PM tasks that were completed on the six element task. Further work by Kliegel et al. (2002) highlights the importance of other EF processes in PM tasks. They found that more than 50% of overall variance on PM tasks could be predicted by individual differences in planning and cognitive flexibility. In specific relation to drug use, Heffernan and Bellis (2012) found that ecstasy-related deficits on the Cambridge PM test (CAMPROMPT) fell to below statistical significance when controlling for central executive scores. In summary of the research outlined above, it appears that PM performance may be related to EF and that the PM deficits observed in ecstasy users may be underpinned by underlying problems in executive functions.

One possible reason for the role of EF processes in PM is that some PM tasks require detailed monitoring processes, especially when individuals are required to search the environment for PM cues and to shift attention from an ongoing task or activity to the retrieval of a delayed intention (Einstein & McDaniel, 2010). These operations have been found to rely on executive processes including monitoring and WM functioning (Smith & Jonides, 1999; Martin et al., 2003). Furthermore, in cases where PM cues are presented in an unfamiliar context, there is an increased need for

individuals to monitor the environment in order to realize a delayed intention. This ultimately increases the engagement of frontal executive processes including planning, attention switching and/or inhibitions (Martin et al., 2003). Another reason why EF ability may mediate performance on PM tasks is that both PM and EF tasks recruit frontal brain operations (Okuda et al., 2007; Collette et al., 2005). For instance, frontal regions have been associated with intention formation, intention retention, intention retrieval and intention execution (Ellis, 1996) in PM tasks. Similarly, several EF operations including shifting, inhibition and monitoring process have been linked to frontal brain regions (Rubia et al., 2009; Shimamura et al., 1991; Wager et al., 2004).

The aim of this Chapter is to investigate the role of EF processes in accounting for PM deficits in ecstasy users. Multiple laboratory-based measures of PM and EF were administered. In relation to PM performance, ecstasy users and non-ecstasy users were compared on the F1 event-based PM task, the delayed-recall PM task, the Karolinska fatigue PM task and the CAMPROMPT. With regard to EF performance, ecstasy users and non-ecstasy users were compared on a number of different laboratory-based measures of shifting, updating and inhibition. The plus/minus task and the number/letter task were both used to measure shifting. The computation span task and the random letter generation (RLG) task were administered to assess updating with the latter also loading on inhibition functions (alphabetical and repeat sequences). The Chicago word fluency task (CWFT) was used as an additional measure of verbal word fluency. Stepwise multiple regression was then performed to investigate the extent to which PM deficits in ecstasy users were attributable to individual differences in shifting, updating, inhibition or verbal word fluency.

10.2 Method

Participants

Forty-two ecstasy users (28 males) and 46 non-ecstasy users (16 males) took part in the investigation (for demographic data, see Table 10.1). There was a significant gender difference between the two groups, $\chi^2(1)=7.90$, $p=.005$ such that there were more males than females in the ecstasy-user group and more females than males in the non-ecstasy user group. Participants were recruited via direct approach to university students. All participants were university students attending Liverpool John Moores University (LJMU) or the University of Central Lancashire (UCLAN). The participants who took part in this investigation were the same as those in Chapter 8. Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence for ecstasy users was 43.46 weeks, median=8.00 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing. The present study was approved by the ethics committees of the University of Central Lancashire and Liverpool John Moores University in accordance with the guidelines of the British Psychological Society.

Materials

Patterns of ecstasy and other drug use were obtained via a background drug use questionnaire (Montgomery et al., 2005, see Appendix 1 for a copy of this questionnaire). For the major illicit drugs, the same measures of long-term drug use (annual average dose per session and frequency of use) were collected as indicated in earlier empirical work (see Chapter 7 & Chapter 8). The current use of cigarettes and alcohol were also assessed. The Raven's Progressive Matrices test (Raven et al., 1998) was used as a measure of fluid intelligence. Daytime sleepiness was measured via the Epworth Sleepiness Scale (Johns, 1991; see Chapter 7: Empirical Chapter 1, section 7.2 for detailed descriptions of these measures; See Appendix 2 for a copy of the Epworth Sleepiness Scale Score questionnaire).

Four laboratory-based measures of PM were administered. The F1 event-based PM task, the long-term delayed recall PM task, and the fatigue PM task were taken from Hadjiefthyvoulou et al. (2011a) and the Cambridge PM test (CAMPROMPT) from

Wilson et al. (2005). A full description of these laboratory-based measures of PM can be found in Chapter 5, section 5.3.

Four further laboratory-based measures were administered to assess different aspects of executive functions including verbal word fluency performance, access to long-term memory, updating, shifting and inhibition.

Verbal word fluency / Access to long-term memory

The Chicago word fluency task (CWFT) was administered which requires participants to write down as many four-letter words as they can, beginning with the letter C during a four-minute period. Once completed, participants are given a further five-minutes to write down as many words as they can, beginning with the letter S. Participants are instructed not to write any place names, people's name or plurals. Two scores are generated and relate to the number of four letter words beginning with the letter C and the number of words beginning with the letter S that were produced. Scores reflect verbal word fluency and the efficiency of access to semantic memory whereby higher scores are indicative of better performance.

Updating

The computation span task requires participants to solve simple arithmetic problems (e.g., 7+3=?). Participants record their responses by circling one of three multiple-choice answers as each problem is presented. Participants are also required to recall the second digit of each presented problem (e.g., 3). Once all problems have been solved, participants are asked to write down the last digit from each computation in serial order. The task begins with three trials with one arithmetic problem and increases by one problem to two, three etc. In order to progress to the next computation level, participants are required to successfully complete each aspect of the task in at least two of the three trials at the current level. Computation span is scored according to the maximum number of end digits recalled in serial order. Participants are also required to have solved the corresponding arithmetic problems correctly. Computation span score reflects the number of serial positions correctly recalled out of a maximum of 63. This task is suggested to load on the updating component of EF.

Shifting

The plus/minus task consists of three lists of 30, two-digit numbers. For the first list, participants are asked to add 3 to each number and to write the answer in a box situated to the right. For the second list, participants are required to subtract three from the two-digit number. Finally, for a third list, participants are required to alternatively add and subtract three from each two-digit number in the list. A stopwatch is used to record the total time it takes for participants to complete each list. Scores are expressed as a ratio with scores above one reflecting an increasing shift cost.

In the number/letter task, participants are presented with a number/letter pair (e.g. D4) in one of four quadrants on a computer screen. If the target is in the top half of the screen, participants are required indicate whether the letter is a vowel (A, E, I, O or U) or a consonant. If the target is in the bottom half of the screen, the task is to indicate if the number is odd or even. In the main task, the target is presented in the top half of the screen for 64 trials, then the bottom half for 64 trials, and then in a clockwise rotation around all four quadrants for a further 64 trials. The trials in the first two blocks require no switching, whereas the third set does. Once again, scores are expressed as a ratio with scores above one reflecting a increasing shift cost.

Inhibition

The random letter generation (RLG) task requires participants to recite letters in a random sequence whilst avoiding alphabetical and well-known letter sequences (e.g. ABC, BBC or TLC) and with the aim of producing each letter with the same overall frequency. Traditionally, this task is repeated three times whereby participants are asked to generate a total of 100 letters at a rate of one letter every four seconds, one letter every two seconds or one per second. However, only the two second trial was used in the present study. Outcomes on the RLG task are divided into four performance measures. Redundancy reflects the extent to which the participant's responses are random in terms of the expected frequency of the occurrence of each letter of the alphabet. A score of zero would indicate that the participant's responses are totally random while a score of one would indicate that the participant has generated the same letter all of the time. Repeat sequences refers to the number of

times that a participant has repeated a letter pair (i.e., how may times has the letter pair, “LV” been repeated). Alphabetical sequences relates to the number of times that consecutive letters of the alphabet are repeated (i.e., AB, FG, LM). In each case, a higher score is indicative of poorer performance. The total number of letters generated is also recorded whereby higher scores are indicative of better performance. The redundancy score on the random letter generation (RLG) is suggested to load on the updating component of EF while the other three remaining RLG measures (repeat sequences, alphabetical sequences, total number of letters generated) reflect the inhibition component of EF (Fisk & Sharp, 2004).

A computer using MS-DOS was used for the F1 event-based PM task, the computation span task, the number/letter task and the RLG task.

Procedure

Participants were informed of the general purpose of the experiment and verbal informed consent was obtained. Background questionnaires assessing age, years of education, general health and other relevant lifestyle variables (arousal, anxiety and depression, daytime sleepiness) were administered first and in a counterbalanced order. The laboratory-based measures of PM and executive functioning listed above were administered in a counterbalanced order. The Karolinska fatigue PM task was administered throughout the test-session.

All tests were administered under laboratory conditions. Participants were fully debriefed and given the opportunity to ask any questions about the study prior to leaving the laboratory. Participants were paid £20 in store vouchers for their participation.

Design/Statistics

All of the demographic and background variables were analysed using a between participant design with user group as the independent variable (ecstasy users and non-ecstasy users). Age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale Score, arousal, anxiety and depression were included as background measures. Any group differences on these background measures were investigated using independent t-test. Total lifetime consumption, total

use in the last 30 days, current frequency of use, duration of drug use and number of weeks since last use were included as background drug use variables for ecstasy, cannabis and cocaine.

For ecstasy, cannabis and cocaine, data for total lifetime consumption, total use in the last 30 days, total use in the last 10 days, current frequency of drug use, duration of drug use and number of weeks since last use were not normally distributed. This was characterised by skew or kurtosis associated with z values exceeding 3.29, $p<.001$. As a result non-parametric analyses were used (Tabachnick & Fidell, 2001).

The F1 event-based PM task, the Karolinska fatigue PM task, the long-term delayed recall PM task and the CAMPROMPT were included as PM dependent variables. The CWFT, the computation span task, the plus/minus task, the number/letter task and the RLG task were included as EF dependent variables. In light of the distributional characteristics of the PM and EF dependent variables, a mix of parametric (independent t-test) and non-parametric tests (Mann-Whitney U test) were employed with drug user group (ecstasy users or non-ecstasy user) as the independent variable.

In the main analyses, stepwise regression was used to determine the extent to which drug-related and other differences on the EF measures may account for drug-related differences on PM measures. Thus, separate regressions were run for each of the PM measures with ecstasy use defined dichotomously (user versus nonuser) and the EF measures as potential independent variables.

10.3 Results

Demographical and Background Variables

The scores for the demographical variables and background variables (including age, intelligence, years of education, cigarette and alcohol consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression) are set out in Table 10.1. The scores for the background drug use variables i.e., total lifetime consumption, total use in the last 30 days, current frequency of use, duration of drug use and number of weeks since last use for ecstasy, cannabis and cocaine are shown in Table 10.2.

Table 10.1 Demographical variables of ecstasy users and non-ecstasy users.

	Ecstasy users		Non-ecstasy users		p
	Mean (SD)	n	Mean (SD)	n	
Age (years)	22.38 (5.24)	42	20.09 (2.12)	44	.009**
Ravens Progressive Matrices (max 60)	45.11 (5.93)	37	44.45 (7.98)	52	.68
Years of education	15.55 (2.25)	41	14.55 (1.81)	42	.03*
Alcohol (units per week)	16.91 (17.33)	37	9.96 (12.11)	42	.04*
Cigarettes per day	6.28 (4.02)	20	6.94 (2.93)	8	.68
Epworth Sleepiness Score	7.23 (3.31)	39	7.72 (3.07)	42	.48
Arousal	19.39 (4.69)	36	19.62 (3.80)	39	.82
Anxiety	11.83 (3.51)	36	11.26 (2.83)	38	.44
Depression	12.50 (2.97)	39	12.54 (2.49)	39	.95

**$p<.01$

Independent t-tests showed that non-ecstasy users were significantly younger, had studied for a significantly shorter period of time and consumed significant less alcohol each week compared to ecstasy users. A series of independent t-tests revealed that the groups did not differ significantly in terms of intelligence, cigarette consumption, Epworth Sleepiness Scale score, arousal, anxiety and depression (see Appendix 6 for detailed statistical analyses related to background variables).

Table 10.2 Background drug use variables of ecstasy users and non-ecstasy users

	Ecstasy users					Non-ecstasy users					p
	Median	Min.	Max.	Int. Range	n	Median	Min.	Max.	Int. Range	n	
Total prior consumption											
Ecstasy (tablets)	56.00	1.00	1078.00	184.00	41	-	-	-	-	-	-
Cannabis (joints)	2877.50	1.00	21240.00	3004.75	34	237.00	14.00	1888.00	1644.25	8	.46
Cocaine (lines)	109.50	4.00	1288.00	346.98	34	23.50	1.00	46.00	-	2	
Total use in the last 30 days											
Ecstasy (tablets)	.00	.00	12.00	.00	39	-	-	-	-	-	-
Cannabis (joints)	.75	.00	480.00	27.00	34	1.50	.00	180.00	38.75	8	.96
Cocaine (lines)	.00	.00	22.50	2.13	34	2.50	.00	5.00	-	2	.
Current frequency of use (number of times per week)											
Ecstasy	.08	.00	1.00	.23	40	-	-	-	-	-	-
Cannabis	.23	.00	7.00	2.48	34	.46	.00	6.00	.93	12	.87
Cocaine	.09	.00	4.00	.33	34	.24	.02	.46	-	1	
Duration of use (in weeks)											
Ecstasy	170.00	.00	572.00	194.00	40	-	-	-	-	-	-
Cannabis	267.88	4.00	935.71	158.00	35	121.50	14.00	472.00	223.92	12	.02*
Cocaine	176.00	.00	488.00	195.22	33	78.00	4.00	152.00	-	2	
Number of weeks since last use											
Ecstasy	8.00	.43	624.00	23.00	41	-	-	-	-	--	
Cannabis	1.00	.00	520.00	11.71	35	2.50	.00	104.00	11.68	12	.96
Cocaine	8.00	.00	780.00	43.00	24	3.00	2.00	4.00	-	2	

*p<.05

Since there were only one or two non-ecstasy cocaine users, group comparisons were only performed on the background drug use variables relating to cannabis use. Table 10.2 shows that ecstasy users had been using cannabis for a longer period of time than non-ecstasy users, U=114.00, *p*=.04. Although non-significant, median lifetime cannabis use was considerably higher for the ecstasy user group relative to the non-ecstasy user group. All other group comparisons relating to the background cannabis use variables were non-significant and are presented in Appendix 6.

Laboratory-based measures

Outcomes for the laboratory-based measures of PM for ecstasy users and non-ecstasy users are summarised in Table 10.3.

Table 10.3 Means, Standard Deviations (SD), Median (Med.), Minimum (Min.), Maximum (Max.) and Interquartile Range (Int. Range) scores for ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall task, the Karolinska fatigue PM task and the Cambridge PM test.

	Ecstasy users						Non-ecstasy users						p
	Mean (SD)	Med.	Min.	Max.	Int. Range	n	Mean (SD)	Med.	Min.	Max.	Int. Range	n	
F1 event-based PM task													
Trial 1 Errors	.58 (1.08)	.00	.00	3.00	.75	40	.14 (.65)	.00	.00	3.00	.00	42	.013*
Trial 2 Errors	.23 (.80)	.00	.00	3.00	.00	40	.18 (.59)	.00	.00	3.00	.00	42	.07
Trial 3 Errors	.18 (.59)	.00	.00	.00	.00	40	.05 (.22)	.00	.00	1.00	.00	42	.34
Total Errors	.98 (1.91)	.00	.00	8.00	1.75	40	.19 (.67)	.00	3.00	3.00	.00	42	.02*
Long-term delayed recall PM task													
Total number of recall tests returned	.78 (1.15)	.00	.00	3.00	2.00	41	1.41 (1.42)	1.00	.00	3.00	3.00	44	.03*
Karolinska fatigue PM task													
Percentage completed in first half of test-session	85.30 (15.13)	83.33	50.00	100.00	20.00	41	91.31 (16.00)	100.00	20.00	100.00	20.00	42	.03*
Percentage completed in second half of test-session	42.04 (21.36)	33.33	.00	100.00	43.34	41	79.92 (27.91)	100.00	.00	100.00	27.09	42	<.001***
Percentage completed overall	62.23 (21.36)	60.00	30.00	100.00	29.42	41	86.09 (17.53)	90.45	27.26	100.00	21.25	42	<.001***
Cambridge PM test													
Event-based PM performance	13.83 (3.90)	15.00	2.00	18.00	4.00	36	16.95 (1.97)	18.00	8.00	18.00	2.00	40	<.001***
Time-based PM performance	13.42 (3.80)	14.00	4.00	18.00	4.00	36	27.25 (6.68)	28.00	8.00	36.00	8.00	40	<.001***
Overall PM performance	27.25 (6.69)	28.00	8.00	36.00	8.00	36	34.15 (3.28)	36.00	20.00	36.00	2.00	40	<.001***

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

The distributions of the data for Trial 1 errors (Skew, z=8.94 and Kurtosis, z=7.73), Trial 2 errors (Skew, z=18.91 and Kurtosis, z=45.39), Trial 3 errors (Skew, z=18.20 and Kurtosis, z=49.10) and total errors (Skew, z=12.09 and Kurtosis, z=21.31) on the F1 event-based PM task, for the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed in the first half of the test-session only, Skew, z=-5.73 and Kurtosis, z=5.87) and for all subscales of the CAMPROMPT (event-based PM total, Skew, z=-6.76 and Kurtosis, z=6.96, time-based PM total, Skew, z=-5.78, Kurtosis, z=3.91, overall PM, Skew, z=-5.86, Kurtosis, z=4.66) deviated significantly from normality. This was characterised by the skew and/or kurtosis z scores exceeding 3.29, $p<.001$ (Tabachnick & Fidell, 2001). Group differences were investigated via Mann-Whitney U tests.

Where the distributions were normal, independent t-tests were used to investigate group differences on two aspects of the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed in the second half of the test-session and overall proportion of Karolinska fatigue questionnaires completed during the first and second half of the test-session) and the long-term delayed recall PM task.

Table 10.3 reveals that ecstasy users made more errors than non-ecstasy users on all trials of the F1 event-based PM task. Group differences were especially pronounced on trial 1 and overall error rate. Group differences were less evident on trail 2 and trail 3 of the F1 event-based PM task. There was a significant difference in the number of errors made on trail 1, U=675.00, $p=.013$ and overall error rate, U=661.00, $p=.02$ between ecstasy users and non-ecstasy users. The group difference in the errors made on trial 2 of the F1 event-based PM task approached statistical significance, U=777.00, $p=.07$ and would have been significant on a one-tailed basis. There was no significant difference between ecstasy users and non-ecstasy users in terms of the number of errors made on trail 3 of the F1 event-based PM task, U=794.00, $p=.34$.

The data in Table 10.3 reveals that non-ecstasy users returned more delayed recall test sheets (long-term delayed recall PM task) than ecstasy users with independent t-test showing that the difference was statistically significant, $t(81,49)=2.25$, $p=.03$.

In relation to more short-term time-based PM performance, Table 10.3 shows that non-ecstasy users successfully completed a greater number of Karolinska fatigue questionnaires during the first and second halves of the test-session compared to ecstasy users. The group difference was sufficiently larger in terms of the number of delayed recall tests sheets completed in the second half of the test-session. Mann-Whitney U test (proportion of Karolinska fatigue questionnaires completed during the first half of the test-session) and independent t-test (proportion of Karolinska fatigue questionnaires completed during the second half of the test-session) confirmed that both group differences were statistically significant, U=650.00, p=.03 and t(81)=5.73, p<.001, respectively. As expected, overall performance on the Karolinska fatigue questionnaire was also better for non-ecstasy users relative to ecstasy users with independent t-test confirming that the difference was statistically significant, t(81)=5.57, p<.001.

Further inspection of the data in Table 10.3 shows that non-ecstasy users successfully completed more event- and time-based PM tasks on the CAMPROMPT compared to ecstasy users with Mann-Whitney U tests indicating that the group differences were statistically significant, U=308.50, p<.001, U=221.50, p<.001, respectively. Overall PM performance on the CAMPROMPT was also significantly better for non-ecstasy users relative to ecstasy users, U=191.50, p<.001.

Table 10.4 Means, Standard Deviations (SD), Median, Minimum (Min.), Maximum (Max.) and Interquartile Range (Int. Range) scores for ecstasy users and non-ecstasy users the Chicago word fluency task, the computation span task, the plus/minus task, the number/letter task and the random letter generation task

	Ecstasy users						Non-ecstasy users						p
	Mean (SD)	Median	Min.	Max.	Int. Range	n	Mean (SD)	Median	Min.	Max.	Int. Range	n	
The CWFT													
Letter C	13.83 (6.95)	14.50	.00	30.00	8.75	40	11.91 (5.48)	10.50	3.00	26.00	7.75	44	.18
Letter S	46.82 (13.73)	44.50	21.00	84.00	16.00	40	40.57 (13.11)	38.50	21.00	81.00	14.50	44	.04*
The computation span task													
Computation span total	50.13 (11.93)	55.50	14.00	63.00	13.75	40	50.30 (11.02)	54.00	24.00	63.00	14.75	40	.84
The plus/minus task													
Shift cost	1.46 (.30)	1.41	.89	2.47	.37	36	1.57 (1.61)	1.61	.90	2.16	.37	40	.08
The number/letter task													
Shift cost	1.48 (.24)	1.44	1.08	2.38	.23	38	1.48 (.30)	1.44	1.13	2.78	.23	42	.69
The RLG task (2 second trial)													
Redundancy	.06 (.04)	.05	.02	.22	.03	34	.06 (.02)	.06	.02	.11	.03	37	.07
Repeat Sequences	11.82 (7.26)	3.00	42.00	7.00	7.00	34	10.70 (4.44)	11.00	2.00	20.00	5.00	37	.90
Alphabetical sequences	10.53 (7.22)	8.00	3.00	37.00	6.00	34	9.43 (4.19)	9.00	.00	17.00	6.50	37	.77
Total number of letters generated	97.26 (4.34)	98.50	81.00	101.00	4.00	34	95.92 (8.27)	99.00	66.00	110.00	6.00	37	.96

*p<.05

The distributions of the data for the letter “C” word fluency task (Skew, z=1.62 and Kurtosis, z=-3.81), computation span total score (Skew, z=-4.70 and Kurtosis, z=1.39), shifting cost on the number letter task (Skew, z=8.13 and Kurtosis, z=13.45) and for all measures of the RLG task (redundancy, Skew, z=8.10 and Kurtosis, z=15.48; repeat sequences, Skew, z=8.15 and Kurtosis, z=18.41; alphabetical sequences, Skew, z=7.50 and Kurtosis, z=12.98; total number of letters generated, Skew, z=-8.39 and Kurtosis, z=13.53) deviated significantly from normality. This was characterised by the skew and/or kurtosis z scores exceeding 3.29, $p<.001$ (Tabachnick & Fidell, 2001). In each case, group differences were investigated via Mann-Whitney U tests. As with the laboratory-based PM measures and where the distributions were normal, independent t-tests were used to investigate group differences on letter “S” word fluency performance and shifting cost on the plus/minus task.

Verbal Fluency/ Access to long-term memory

Contrary to expectation, the data in Table 10.4 reveals that ecstasy users successfully produced more four letter words beginning with the letter “C” than non-ecstasy users. However, Mann-Whitney U test showed that the group difference was not significant, U=730, $p=.18$. Also contrary to expectation, ecstasy users produced more words beginning with the letter “S” than non-ecstasy users with independent t-test showing that the group difference was statistically significant, $t(82)=2.14$, $p=.04$.

Updating

In relation to updating executive performance, the data in Table 10.4 shows that ecstasy users and non-ecstasy users correctly recalled a similar number of serial positions on the computation span task with Mann-Whitney U test confirming that there was no significant difference between the groups, U=779.00, $p=.84$. This finding was not expected.

With respect to the redundancy scores on the RLG task which may reflect updating executive performance (Miyake et al., 2000), the group means and medians were similar for ecstasy users and non-ecstasy users. Nonetheless, further examination of

the maximum values in Table 10.4 show that ecstasy users had higher redundancy scores on the RLG task compared to non-ecstasy users. The group difference was statistically borderline, U=468.50, *p*=.07.

Shifting

In relation to the plus/minus task, ecstasy users demonstrated a lower shifting cost than non-ecstasy users. The group difference was statistically borderline, t(72.51)=1.76, *p*=.08. Similar shifting costs were found between ecstasy users and non-ecstasy users on the number/letter task with Mann-Whitney U test showing that there was no significant difference between the groups, U=738.00, *p*=.69.

Inhibition

As stated previously, repeat sequences, alphabetical sequences and total number of letters generated are suggested to load on the inhibition component of executive functions. The data in Table 10.4 reveals that ecstasy users produced slightly more repeat sequences and alphabetical sequences on the RLG task. However, the group differences were not significant, U=618.00, *p*=.90 and U=603.50, *p*=.77, respectively. Table 10.4 also shows that ecstasy users and non-ecstasy users generated a similar number of letters on the two second trial of the RLG task. Mann-Whitney U test confirmed that there was no significant difference between the groups, U=625.00, *p*=.96).

Stepwise multiple regression was performed to determine the extent to which each of the PM outcomes (i.e., performance on the F1 event-based PM task, the long-term delayed recall PM task, the Karolinska fatigue PM task and the Cambridge PM test) are predicted by ecstasy use and each of the EF outcomes (e.g., the CWFT, the computation span task, the plus/minus task, the number/letter task and the RLG task) and more importantly the extent to which ecstasy-related variance in the PM measures overlaps with the EF outcomes.

For each PM outcome, in the first step, ecstasy use (coded dichotomously as user versus nonuser) was included in the regression analysis. In the second step, the EF measures were then entered in a stepwise manner. In a second series of regressions,

the EF measures were first entered in a stepwise manner prior to the inclusion of the ecstasy use variable in the second step. Significant predictors of each of the PM outcomes are shown in Table 10.5, Table 10.6, Table 10.7, Table 10.8, and Table 10.9.

Table 10.5 Stepwise regression for outcomes on F1 event-based PM task when ecstasy use is submitted prior to the executive functioning measures and vice versa.

	The F1 event-based PM task											
	Errors made on Trial 1				Errors made on Trial 2				Errors made on Trial 3			
	Beta	t	p	Partial Correlation	Beta	t	p	Partial Correlations	Beta	t	p	Partial Correlations
Model 1 (ecstasy use first)												
Ecstasy use	-.239	-1.973	.053	.057	-.200	-1.630	.108	.040	-.144	-1.165	.248	.021
R^2/F	.057; (1,64)=3.89, *p*=.053				.040; (1,64)=2.67, *p*=.11				.021; (1,64)=1.36, *p*=.25			
Model 1 (EF measures first)												
RLG (repeat sequences)	.291	2.433	.018*	.085								
RLG (alphabetical sequences)					.400	3.495	.001**	.160				
Ecstasy use									-.144	-1.165	.248	.021
R^2/F	.085; (1,64)=5.92, *p*=.02*				.160; (1,64)=12.21, *p*=.001**				.021; (1,64)=1.36, *p*=.25			
Model 2 (ecstasy use or EF measures first)												
RLG (repeat sequences)	.270	2.290	.025*	.072								
RLG (alphabetical sequences)					.385	3.372	.001**	.147				
Ecstasy use	-.213	-1.808	.075	.045	-.163	-1.430	.158	.027				
R^2/F	.130; (2,63)=4.70, *p*=.013*				.187; (2, 63)=7.23, *p*=.001**							

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

Table 10.6 Stepwise regression for outcomes on the F1 event-based PM task when ecstasy use is submitted prior to the executive functioning measures and vice versa (continued).

	The F1 event-based PM task			
	Overall error rate			
	Beta	t	p	Partial Correlations
Model 1 (ecstasy use first)				
Ecstasy use	.269	-.236	.029*	.072
R^2/F	.072; (1,64)=5.00, *p*=.03*			
Model 1 (EF measures first)				
RLG (alphabetical sequences)	.324	2.742	.008**	.105
R^2/F	.105; (1,64)=7.52=.01**			
Model 2 (ecstasy use or EF measures submitted first)				
RLG (alphabetical sequences)	.301	2.602	.102	.090
Ecstasy use	-.241	2.742	.008**	.105
R^2/F	.162; (2,63)=6.11, *p*=.004**			

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

Table 10.7 Stepwise regression for outcomes on the Karolinska fatigue PM task when ecstasy use is submitted prior to the executive functioning measures and vice versa.

	Karolinska fatigue PM task											
	% completed in the 1st half of the session				% completed in the 2nd half of the session				% completed overall			
	Beta	t	p	Partial Correlations	Beta	t	p	Partial Correlations	Beta	t	p	Partial Correlations
Model 1 (ecstasy use first)												
Ecstasy use	.192	1.562	.123	.037	.537	5.09	<.001***	.288	.526	4.949	<.001***	.277
R^2/F	.037 ;	(1,64)=2.44, *p*=.123			.288;	(1,64)=25.91, *p*<.001***			.277;	(1,64)=24.50, *p*<.001***		
Model 1 (EF measures first)												
RLG (redundancy)	.283	2.356	.022*	.080								
Shift Cost (number/letter task)					-.248	-2.052	.044*	.062	-.256	-2.123	.038*	.066
R^2/F	.080;	(1,64)=5.55, *p*=.02*			.062;	(1,64)=4.21, *p*=.04*			.066;	(1,64)=4.51, *p*=.03*		
Model 2 (ecstasy use first)												
Ecstasy use	.174	1.462	.149	.030	.537	5.29	<.001***	.288	.526	5.156	<.001***	.277
RLG (redundancy)	.271	2.278	.026*	.073								
Shift cost (number/letter task)					-.249	-2.45	.017*	.062	.257	-2.519	.014*	.066
R^2/F	.110;	(2,63)=3.90, *p*=.03*			.350;	(2,63)=16.98, *p*<.001***			.343;	(2,63)=16.44, *p*<.001***		
Model 2 (EF measures first)												
RLG (redundancy)	.285	2.437	.018*	.081								
Shift Cost (number/letter task)	-.243	-2.080	.042*	.059	-.249	-2.454	.017*	.062	-.257	-2.519	.014*	.066
Ecstasy use					.537	5.290	<.001***	.288	.526	5.156	<.001***	.277
R^2/F	.139;	(2,63)=5.08, *p*=.01*			.350;	(2,63)=16.98, *p*<.001***			.343;	(2,63)=16.44, *p*<.001***		
Model 3 (ecstasy use first)												
Ecstasy use	.236	1.998	.050	.052	.557	5.61	<.001***	.308	.546	5.445	<.001***	.294
RLG (redundancy)	.317	2.717	.009**	.097	.209	2.092	.041 *	.042				
Shift cost (number/letter task)					-.236	-2.26	.027*	.051	-.235	-2.341	.022*	.055
CWFT (S letter)	.281	2.351	.022*	.073								
RLG (repeat sequences)									.202	1.999	.050	.040
R^2/F	.183;	(3,62)=4.63, *p*=.01**			.393;	(3,62)=13.39, *p*<.001***			.383;	(3,62)=12.82), *p*<.001***		
Model 3 (EF measures first)												
RLG (redundancy)	.274	2.360	.021*	.075								
Shift Cost (number/letter task)	-.243	-2.103	.040*	.059								
Ecstasy use	.175	1.503	.138	.030								
R^2/F	.129;	(3,62)=4.21, *p*=.01*										

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

Table 10.8 Stepwise regression for outcomes on the long-term delayed recall PM task when ecstasy use is submitted prior to the executive functioning measures and vice versa.

	Number of delayed recall test sheets returned on the long-term delayed recall PM task			
	Beta	t	p	Partial Correlations
Model 1 (ecstasy use or EF measures first first)				
Ecstasy use	.238	1.960	.054	.057
R^2/ F	.057; (1,64)=3.84, *p*=.054			

Table 10.9 Stepwise regression for outcomes on the Cambridge PM test when ecstasy use is submitted prior to the executive functioning measures and vice versa.

	The Cambridge PM test											
	Event-based PM performance				Time-based PM performance				Overall PM performance			
	Beta	t	p	Partial Correlations	Beta	t	p	Partial Correlations	Beta	t	p	Partial Correlations
Model 1 (ecstasy use first)												
Ecstasy use	.461	25.279	<.001***	.212	.536	4.956	<.001***	.287	.559	5.267	<.001***	.313
R^2/ F	.212; (1,61)=16.44, *p*<.001***				.287; (1,61)=24.56, *p*<.001***				.313; (1,61)=27.74, *p*<.001***			
Model 1 (EF measures first)												
Computation span total	.363	3.039	.003**	.131	.250	2.014	.048*	.062	.352	2.934	.005**	.124
R^2/ F	.131; (1,61)=9.23, *p*<.01**				.062; (1,61)=4.06, *p*=.048*				.124; (1,61)=8.61, *p*<.01**			
Model 2 (ecstasy use or EF measures first)												
Computation span total	.359	3.426	<.01**	.131	.246	2.354	.022*	.061	.347	3.574	<.01**	.120
Ecstasy use	.458	4.371	<.001***	.210	.534	5.119	<.001*	.285	.556	5.725	<.001***	.309
R^2/ F	.341; (2,60)=15.54, *p*<.001***				.347; (2,60)=15.97, *p*<.001***				.433; (2,62)=22.93, *p*<.001***			

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

10.4 Discussion

With regard to both event- and time-based PM, ecstasy users displayed significantly worse performance than non-ecstasy users. Clear event-based PM deficits were observed in ecstasy users on the F1 event-based PM task (trial 1 and overall). Ecstasy users also completed significantly fewer event-based PM tasks on the CAMPROMPT relative to non-ecstasy users. Both short- and long-term time-based PM deficits were found in ecstasy users. In terms of short-term time-based PM performance, ecstasy users remembered to complete significantly fewer Karolinska fatigue questionnaires and also remembered to complete significantly fewer time-based PM tasks on the CAMPROMPT relative to non-ecstasy users. Long-term time-based PM deficits were also observed with non-ecstasy users remembering to return significantly more delayed recall test sheets than ecstasy users in the weeks that followed the test-session. These findings are largely consistent with previous literature (Hadjiefthyvoulou et al., 2011a; 2011b). The ecstasy-related deficits found in PM here are unsurprising since the participants included in this study are the same as those who were used in Empirical Chapter 2 (Chapter 8) where impairments were also observed.

In terms of EF performance, no ecstasy-related deficits were observed in verbal word fluency or long-term memory (The CWFT). In fact, ecstasy users demonstrated superior performance to non-ecstasy users on the CWFT (S-letter fluency). It might be that ecstasy use facilitates verbal fluency in some way. One possibility is that ecstasy increases openness (Gouzoulis-Mayfrank & Daumann, 2006), a personality trait that has been associated with enhanced verbal fluency (Sutin et al., 2011). This finding was unexpected and is not consistent with previous research. Montgomery et al. (2005b) found that ecstasy users performed significantly worse than non-ecstasy users on the CWFT (C and S letter fluency) and, in doing so displayed clear impairments in verbal word fluency and long-term memory. Despite these findings, there is a body of research that suggests that ecstasy use does not significantly impair verbal word fluency (Klugman et al., 1999; Morgan et al., 2002; Wareing et al., 2000). The current findings support the proposal that verbal word fluency is generally unaffected by the use of ecstasy.

On the basis of Miyake et al's (2000) conceptual framework of executive

functions, the current study investigated the extent to which ecstasy use might impair updating, shifting and inhibition executive processes. Ecstasy users performed comparably to non-ecstasy users on the computation span task with each group correctly recalling a similar number of serial positions. While this finding is indicative of normal updating performance in ecstasy users, other studies report very different results. Wareing et al. (2004) found that current and previous ecstasy users were significantly impaired on the computation span task with both groups remembering to recall fewer serial positions than non-ecstasy users. These findings have been replicated in a number of other studies (Fisk, Montgomery, Murphy & Wareing, 2004; Fisk & Montgomery, 2009; Montgomery et al., 2005b) leading to a general consensus that ecstasy use is detrimental to updating EF. Another measure of updating that was used in the current study was the RLG task. Although ecstasy users showed higher redundancy scores relative to non-ecstasy users, this difference failed to reach statistical significance. This finding is consistent with other research that has failed to find ecstasy-related deficits in updating using the RLG task. Montgomery et al. (2005b) did not show ecstasy-group related differences in redundancy scores on the RLG task. A similar pattern of results emerged from Fisk and Montgomery's (2009) research. They found that heavy ecstasy users, light ecstasy users and non-ecstasy users recorded similar redundancy scores of all trials of the RLG task (four second, two second and one second trials). With regard to the current study, the absence of ecstasy-related impairments on the redundancy measure of the RLG task may simply be because this task does not assess updating performance at all. This view is consistent with Miyake et al. (2000) who suggest that random number generation but not random letter generation loads on to the updating component. Fisk and Sharp (2004) also argue that RLG task is demonstrative of the inhibition function and not of the shifting or updating components.

Data from the plus/minus task and the number/letter task failed to show evidence of shifting EF deficits in ecstasy users. Other studies that have used these measures have also shown no effect of ecstasy use on shifting EF performance (Montgomery et al., 2005b). Although some studies that have used alternative measures of shifting (modified versions of the Stroop task; Dafters, 2006) and have demonstrated ecstasy-related impairments (Dafters, 2006), the overall view within the literature is that shifting executive performance is relatively unaffected by ecstasy use

(Murphy et al., 2009). The absence of an association between ecstasy use and performance on the plus/minus task and the number/letter task in the current study support this proposal.

The current study did not show any differences between ecstasy users and non-ecstasy users on the inhibition components of the RLG task (alphabetical sequences, repeat sequences and total number of letters generated). This finding is generally consistent with previous literature that has failed to identify inhibition impairments in ecstasy users using the RLG task (Fisk & Montgomery, 2009; Fisk et al., 2004). In Fisk et al's study, current ecstasy users and non-ecstasy users generated a similar number of alphabetical sequences and repeat sequences on the one-second, two-second and four-second trials of the RLG task. Fisk and Montgomery (2009) replicated these findings in a more recent study and the general consensus in the literature appears to be that the inhibition component of executive functions are generally unaffected by ecstasy use (Murphy et al., 2009; Parrott, 2013).

Stepwise regression was used to determine the extent to which ecstasy-related differences on the EF measures (The CWFT, the computation span task, the plus/minus task, the number/letter task and the RLG task) might account for ecstasy-related differences on PM measures. In relation to this and for the majority of the PM outcomes (all except trial 2 of the F1 event-based PM task where 1.3% of the ecstasy-related variance (4 %) was accounted for by EF measures) the variance accounted for by ecstasy use was largely independent of that associated with the executive function measures. Thus, the effects of ecstasy use on PM performance appear to be independent of any effects associated with the executive measures. These findings are consistent with other research that has shown no link between self-reported EF and PM performance in ecstasy users (Hadjiefthyvoulou et al., 2011c).

The overall findings from Chapter 10 show that EF is not impaired in ecstasy users and that Miyake et al's (2000) sub-processes of updating, shifting and inhibition are not implicated in ecstasy-related PM deficits. Nonetheless, PM impairments in ecstasy users might be underpinned by some other aspect of EF which was not identified by Miyake et al. (2000). For example, the possible role of divided attention in PM task performance should be acknowledged. The completion of event- and time-based PM tasks require individuals to divide attention between the completion of an

ongoing task and remembering to retrieve a PM intention upon the presentation of a target cue or after a period of time has elapsed, respectively. As such, it could be argued that PM deficits in ecstasy users are mediated by involvement of divided attention in PM tasks.

A number of limitations must be acknowledged in relation to the current study. As noted earlier, the ecstasy users who took part in this study also participated in the studies documented in Empirical Chapter 2 (Chapter 8). Thus, the same significant group differences in age and number of years of education that were found in Chapter 8 were also found here. That is, ecstasy users were significantly older than non-ecstasy users and had also studied for a significantly longer period of time relative to non-ecstasy users. As discussed in Chapter 8, it is very unlikely that the ecstasy-related impairments observed in PM are related to differences in age and/or years of education (see Chapter 8 for details).

A further limitation of the current findings is that the weekly average dose of alcohol use was significantly higher for ecstasy users relative to non-ecstasy users. Alcohol has been shown to be detrimental to PM performance (Griffiths et al., 2012; Heffernan et al. 2002) and as such, the possibility that the observed deficits might partly be attributable to alcohol use cannot be excluded. On a similar note, the absence of control groups (cannabis-only users, cocaine-only users, etc.) makes it is difficult to conclude that PM deficits in ecstasy users are attributable to ecstasy use alone. The empirical work in Chapter 11 will use correlation analyses to control for cannabis and cocaine use with respect to PM deficits in ecstasy users.

Although the current study adopted a Stepwise regression approach to investigate the extent to which PM deficits in ecstasy users are mediated by underlying impairments in EF, it is important to acknowledge the problems associated with this method of analysis. Harrel (2001) notes the issue of collinearity between independent variables and subsequent collinearity in the regression model. In the current study, each of the EF measures were included as potential independent variables. However, it is likely that each of the EF measures used in this Chapter (especially those which map onto the same EF's of updating, shifting and inhibition) are strongly correlated with each other. In specific relation to the Stepwise procedure that was adopted in this Chapter, Harrel (2001) suggests that collinearity makes the

independent variables (EF measures) compete for inclusion in the regression model leading to the arbitrary inclusion of “important” variables. This is further problematic in that it can reduce the stability of parameter estimates, inflate standard errors and reduce the power of corresponding statistical tests (Harrel, 2001). In consideration of this, a heirarchical approach to the regression may have been more appropriate. Unlike Stepwise regression where independent variables compete for inclusion in the regression model, hierarchical regression is a sequential process where variables are entered into the regression model based on underlying theory. By including specific independent variables at the first stage of the regression and then adding others at subsequent stages, researchers can examine the specific contribution of individual independent variables. Nonetheless, it is worthy of note that the current study did in fact adopt a hierarchical approach overall since ecstasy use was included in either the first or last stage and the EF variables in the other stage. Furthermore, due to the overlapping variance between the EF measures included in this study, their inclusion altogether may have resulted in none individually being significant. Nonetheless, as with all Stepwise procedures some degree of caution should be taken in interpreting the results especially given the degree of collinearity between the EF measures.

To conclude, the current study found clear ecstasy-related deficits in event- and time-based PM but failed to identify impairments in updating, shifting or inhibition executive processes. Stepwise regression showed that ecstasy-related differences on EF measures were unrelated to ecstasy-related impairments on PM outcomes.

Chapter 11: The relationship between long- and short-term indicators of ecstasy, cannabis and cocaine use and prospective memory.

Chapter 11 used Pearson's correlations to investigate the relationship between long- (total lifetime consumption, long-term average dose per session, long-term average frequency of use, duration of use for ecstasy, cannabis and cocaine) and short-term (total use in the last 12 months, mean average dose per session in the last 12 months, mean average frequency of use in the last 12 months, current frequency of use and number of weeks since last use for ecstasy, cannabis and cocaine) indicators of drug use on laboratory-based measures of Prospective Memory (PM; The F1 event-based PM task, the Karolinska fatigue PM task and the Karolinska fatigue PM task) in a sample of polydrug users who were primarily identified by their ecstasy use. Partial correlations were then performed to investigate whether long-term drug-related impairments in PM remain statistically significant after controlling for the long-term indicators of other drug use and aspects of recent use.

11.1 Introduction

The empirical work outlined in Chapter 7, Chapter 8 and Chapter 10 provide evidence for ecstasy-related deficits in prospective memory (PM). However, one of the main limitations of this work is that other drug has not been controlled for. Thus, it remains unclear as to whether the PM impairments found in ecstasy users are attributable to ecstasy use or due to the use of other illicit drugs such as cannabis and cocaine.

Cannabis use has been associated with PM deficits on a range of self-report (Cuttler et al., 2012; Fisk and Montgomery, 2008; Rodgers et al., 2001) and laboratory-based tasks (McHale & Hunt, 2008; Hadjiefthyvoulou et al., 2011a; Hadjiefthyvoulou et al., 2011b). Cuttler and co-workers (2012) used the Prospective Memory Questionnaire (PMQ; Hannon et al., 1995) to investigate self-reported PM performance in chronic cannabis users, moderate cannabis users and non-drug users. The PMQ provides measures of three classes of PM including short-term habitual PM, long-term episodic PM and internally cued PM. Relative to moderate cannabis users and non-drug users, chronic cannabis users reported deficits in internally cued PM. Further self-reported deficits were observed in Fisk and Montgomery's (2008) study. They also used the PMQ and found evidence of self-reported short-term

habitual, long-term episodic and internally cued PM impairments in cannabis users. In relation to more objective PM performance, McHale and Hunt (2008) used the Rivermead Behavioural Memory task (RBMT; Wilson et al., 1985) to investigate event-based PM performance (The *Belonging* subset) in a sample of cannabis users, tobacco smokers and non-drug users. Other measures of short- and long-term time based performance were used whereby participants were required to press a timer, 10-minutes after being instructed to do so and to post a letter back to the experimenter 2-days after the test-session, respectively. McHale and Hunt (2008) found that chronic cannabis users were significantly impaired in short- and long-term time-based PM relative to moderate cannabis users and non-drug users. Although, no evidence of event-based PM deficits were observed, other studies have found cannabis-related impairments on the *Message* subset of the RBMT. Hadjiefthyvoulou et al. (2011a) who also used the RBMT and found that frequency of cannabis use was associated with unique variance on the event-based, *Message* subset of the RBMT. Specifically, increased frequency of cannabis use was associated with poorer performance on both PM measures. Hadjiefthyvoulou et al. (2001b) also found that increased cannabis consumption in the previous 30 days and increased frequency of cannabis use was associated with poor performance on event-based PM tasks of the Cambridge PM test (Wilson et al., 2005).

Recent research has also found evidence of PM deficits in cocaine users. Hadjiefthvoulou et al. (2011a) found that overall lifetime cocaine consumption correlated significantly with performance on a range of laboratory-based PM tasks including the *Appointment* (time-based PM) and *Belonging* subscales (event-based PM) of the RBMT, the Karolinska fatigue PM task and the long-term delayed recall PM task in a group of ecstasy/polydrug users. Frequency of cocaine use was also related to performance on the *Appointment* and *Belonging* subscales of the RBMT task, the Karolinska fatigue PM task, the F1 event-based PM task and the long-term delayed recall PM task. Increased frequency of cocaine use was associated with worse performance in all cases. While the polydrug user group was primarily identified by ecstasy use, cocaine use was found to be an important factor in the event-and time-based PM deficits that were found. In another study by Hadjiefthyvoulou et a.l (2011b), a clear relationship was found between cocaine use and event-based PM performance on the CAMPROMPT (Hadjiefthyvoulou et al., 2011b). Specifically,

increased lifetime dose, greater consumption in the last 30 days and increased frequency of use were all associated with poorer event-based PM performance on the CAMPROMPT.

Considering the evidence presented in the paragraphs above, it is plausible that the ecstasy-related deficits found in PM might be mediated by the use of cannabis and/or cocaine. The current study used Pearson's correlations to investigate the relationship between long- (total lifetime consumption, long-term average dose per session, long-term average frequency of use, duration of use for ecstasy, cannabis and cocaine) and short-term (total use in the last 12 months, mean average dose per session in the last 12 months, mean average frequency of use in the last 12 months, current frequency of use and number of weeks since last use for ecstasy, cannabis and cocaine) indicators of drug use on laboratory-based measures of PM (The F1 event-based PM task, the long-term delayed recall PM task and the Karolinska fatigue PM task) in a sample of polydrug users who were primarily identified by their ecstasy use. Importantly, non-users of specific drugs were excluded from the exploratory correlations between long- and short-term indicators of drug use and PM outcomes. Thus, any significant correlations are likely to be attributable to trends within the drug using participants rather than due to the absence of use in drug naïve participants. A number of partial correlations were then performed to determine whether long-term drug-related impairments in PM remain statistically significant when controlling for the long-term indices of other drug use and aspects of recent use. It was predicted that increasing levels of illicit drug use would be associated with worse performance on PM measures. Period of abstinence was expected to be positively associated with PM performance.

11.2 Method

Design

Correlational analysis was used with long- and short-term indicators of drug use being correlated with laboratory-based measures of PM. Partial correlations were then performed controlling for long-term indices of other drug use and the effects of recent drug use. Partial correlations were based solely on the zero order correlations that were significant (both in terms of the association being tested and the controls introduced). Since predictions were directional in nature, one-tailed probability values are reported.

Participants

This study uses data collected and reported in previous chapters (Chapter 7, Chapter 8 and Chapter 10). A total of 181 participants consisting of polydrug users and non-drug users took part in the current investigation. Participant details are reported in previous chapters.

The participants whose data is used in this study were recruited via direct approach. All participants were university students attending Liverpool John Moores University (LJMU) or The University of Central Lancashire (UCLan). Participants were requested to refrain from ecstasy use for at least 10 days prior to the test-session (the mean period of abstinence for ecstasy/polydrug users was 45.01 weeks, median=8.00 weeks). Ecstasy/polydrug users were also asked to refrain for the use of other illicit drugs for at least 24 hours and ideally seven days prior to testing. The present study was approved by the ethics committees of the University of Central Lancashire and Liverpool John Moores University in accordance with the guidelines of the British Psychological Society.

Materials

Patterns of ecstasy, cannabis and cocaine were obtained via a background drug use questionnaire (Montgomery et al., 2005, see Appendix 1 for a copy of this questionnaire). For each drug, the same measures of long- (annual average dose per session and frequency of use) and short-term (average dose per session for each month in the 12 months prior to the test-session and frequency of use) drug use were

collected. With regard to long-term indices of drug use, estimates of total lifetime use for ecstasy, cannabis and cocaine and their average frequency of use (times per week) were calculated together with the mean average dose per session and the duration of use. In relation to short-term indices of ecstasy, cannabis and cocaine use, estimates of total use in the 12 months prior to the test-session and the average frequency of use during the previous 12 months were calculated. For each drug, data relating to the mean average dose per session in the previous 12 months was calculated together with current frequency of use and period of abstinence.

Procedure

Participants were informed of the general purpose of the experiment and verbal informed consent was obtained. Three laboratory measures of PM were administered including the F1 event-based PM task (Hadjiefthyvoulou et al., 2011a), the long-term delayed recall PM task (Hadjiefthyvouolou et al., 2011a) and the Karolinska fatigue PM task (Hadjiefthyvoulou et al., 2011a). A computer using MS-DOS was used for the F1 event-based PM task. Full descriptions of all laboratory measures of PM can be found in Chapter 5. These measures were administered in a counterbalanced order. Finally, the background drug use questionnaire was administered.

All tests were administered under laboratory conditions. Participants were fully debriefed and given the opportunity to ask any questions about the study prior to leaving the laboratory. Participants were paid £20 in store vouchers for their participation.

11.3 Results

Inter-correlations between the F1 event-based PM task, the long-term delayed recall PM task and the Karolinska fatigue PM task.

The F1 event-based PM task, the long-term delayed recall PM task and the Karolinska fatigue PM task were included in the current study to investigate short-term event-based PM, long-term time-based PM, and short-term time-based PM performance, respectively, in a sample of polydrug users. Inter-correlations were performed to examine the relationship between these laboratory-based measures of PM. Inspection of the data in Table 11.1 shows that the F1 event-based PM task, the long-term delayed recall PM task and the Karolinksa fatigue PM task were not inter-correlated with each other.

Table 11.1 Inter-correlations between the F1 event-based PM task, the long-term delayed recall PM task and the Karolinska fatigue PM task.

	F1 event-based PM task				**The long-term delayed recall task**	**The Karolinksa fatigue PM task**		
	Trial 1 errors	Trial 2 errors	Trial 3 errors	Total errors	Total number of recall tests returned	Percentage completed in first half of test-session	Percentage completed in second half of test-session	Percentage completed overall
F1 event-based PM task								
Trial 1 errors		.37***	.19*	.84***	.04	.03	-.09	-.05
Trial 2 errors	.37***		.54***	.77***	-.03	-.06	.04	.03
Trial 3 errors	.19*	.54***		.62***	.03	-.08	-.02	-.05
Total errors	.84***	.73***	.62***		.02	-.03	-.05	-.04
The long-term delayed recall task								
Total number of delayed recall tests returned	.04	-.03	.03	.02		.09	.09	.13
The Karolinska fatigue PM task								
Percentage completed in first half of the test-session	.03	-.06	-.08	-.03	.09		.36**	.37***
Percentage completed in second half of test-session	-.09	.04	-.02	-.05	-.09	.26**		.89
Percentage completed overall	-.05	.03	-.05	-.04	.13	.57***	.89***	

*p<.05, **p<.01, ***p<.001, two-tailed , *Note:* The inter-correlations between the F1 event –based PM task the long-term delayed recall task, between the F1 event-based PM task and the Karolinska fatigue PM task and between the long-term delayed recall task and the Karolinska fatigue PM task were based on data from 175, 173 and 174 participants respectively.

The extent to which long-term indices of ecstasy, cannabis and cocaine use were associated with performance on the F1 event-based PM task, the long-term delayed recall PM task and the Karolinska fatigue questionnaire in a sample of polydrug users were examined. The means and standard deviations for each PM outcome for polydrug users consuming ecstasy, cannabis and cocaine users are shown in Table 11.2. Means and standard deviations for long-term indices of ecstasy, cannabis and cocaine use are shown in Table 11.3.

Table 11.2. Means and standard deviations for polydrug users consuming ecstasy, cannabis and cocaine on the laboratory-based PM measures.

	Polydrug users consuming:					
	Ecstasy, n=93		Cannabis, n=111		Cocaine users, n=78	
	Mean	SD	Mean	SD	Mean	SD
F1 event-based PM task						
Trial 1 errors	.60	1.11	.61	1.12	.50	1.04
Trial 2 errors	.21	.74	.17	.66	.21	.71
Trial 3 errors	.18	.56	.14	.50	.19	.58
Total errors	.99	1.82	.92	1.69	.90	1.83
Long-term delayed recall PM task						
Total number of recall tests returned (max of 3)	.99	1.27	1.06	1.29	.94	1.26
Karolinska fatigue PM task						
Percentage completed in first half of test-session	87.00	17.17	87.17	17.80	86.10	17.89
Percentage completed in second half of test-session	48.10	31.41	52.63	32.17	47.69	30.07
Percentage completed overall	66.56	20.71	69.16	20.12	65.86	20.19

Note: n for ecstasy users and cannabis users is variable such that only 92 ecstasy and 110 cannabis users completed the F1 event-based PM task and only 90 ecstasy users and 107 cannabis users completed the Karolinska fatigue PM task

Table 11.3 Means and standard deviations for long-term indices of illicit drug use.

	Polydrug Users		
	Mean	SD	n
Total Prior Consumption			
Ecstasy (tablets)	391.87	1445.22	83
Cannabis (joints)	1467.35	2873.13	101
Cocaine (lines)	486.42	967.07	70
Long-Term Average Dose Per Session			
Ecstasy (tablets)	2.56	1.86	83
Cannabis (joints)	1.29	1.64	101
Cocaine (lines)	5.29	6.21	70
Long-Term Average Frequency (times per week)			
Ecstasy	.33	.43	83
Cannabis	1.29	1.64	101
Cocaine	.38	.78	74
Duration of use (weeks)			
Ecstasy	191.47	156.64	83
Cannabis	258.97	178.80	109
Cocaine	168.07	137.63	71

Table 11.4 Associations between long-term indices of ecstasy, cannabis and cocaine use and PM outcomes.

	Zero order correlations with:							
	F1 event-based PM task				The long-term delayed recall task	The Karolinksa fatigue PM task		
	Trial 1 errors	Trial 2 errors	Trial 3 errors	Total errors	Total number of recall tests returned	Percentage completed in first half of test-session	Percentage completed in second half of test-session	Percentage completed overall
Drug use (User coded 0; Nonuser coded 1)								
Ecstasy	-.13*	-.13*	-.13*	-.17*	.15*	.08	.41***	.38***
Cannabis	-.18**	-.08	-.07	-.17*	.12	.09	.35***	.33***
Cocaine	-.03	-.11	-.15	-.10	.16*	.12	.39***	.37***
Long-term indices of drug use								
Total Prior Consumption								
Ecstasy (tablets)	.26**	-.08	-.04	.11	-.06	.02	-.13	-.08
Cannabis (joints)	-.13	-.003	.00	-.08	-.05	-.13	-.06	-.13
Cocaine (lines)	-.03	-.11	-.15*	-.10	.17*	-.21*	-.15	-.19
Long-Term Average Dose Per Session								
Ecstasy (tablets)	.15	-.10	.004	.05	-.08	-.22*	-.22*	-.24*
Cannabis (joints)	-.10	-.01	-.04	-.08	-.08	-.07	-.07	-09
Cocaine (lines)	.24*	-.14	-.17	.02	.14	-.26*	-.24*	-.30*
Long-Term Average Frequency (times per week)								
Ecstasy	.05	-.20*	-.05	-.07	.16	.02	-.08	-.02
Cannabis	-.05	.03	.10	.01	.01	-.02	-.17*	-.17*
Cocaine	-.02	-.01	-.003	-.02	.04	-.21*	-.10	-.16
Duration of use (weeks)								
Ecstasy	.13	-.04	.07	.09	-.12	-.08	-.10	-.11
Cannabis	.08	.08	.16	.13	.13	.01	-.07	-.08
Cocaine	-.03	-.11	-.15*	-.10	.12	-.06	-.03	-.04

*p<.05, **p<.01, ***p<.001, one-tailed.

Correlations between long-term indices of drug use and PM outcomes

Ecstasy

Inspection of Table 11.4 reveals that ecstasy use (defined dichotomously as user versus nonuser) was significantly associated with all but one of the PM measures. Given the manner in which the drug use variable was coded this means that ecstasy use is associated with worse PM performance in all cases. Limiting the analysis to the ecstasy users within the sample, with regard to the more refined measures of ecstasy use, there was a significant and positive correlation between total lifetime ecstasy consumption and the number of errors that were made on trial 1 of the F1 event-based PM tasks. As expected, there was a tendency for the number of event-based PM errors on the F1 event-based PM task to increase with higher total ecstasy consumption. The long-term average dose of ecstasy per session was significantly and negatively associated with all three PM measures of the Karolinska fatigue PM task. This finding is in line with initial predictions and indicates that as the typical dose of ecstasy per session increased, the proportion of Karolinska fatigue questionnaires completed during the first half, the second half and over the entire test-session decreased. There was a significant and negative correlation between the long-term average frequency of ecstasy use per session and the number of errors that were made on trial 2 of the F1 event-based PM task. This finding was not expected and suggests that individuals who use ecstasy less frequently make more event-based PM errors on the F1 event-based PM task.

Cannabis

There was a significant and negative correlation between cannabis use (again defined dichotomously) and the number of errors that were made on trial 1 and overall on the F1 event-based PM task. On this basis, cannabis use was also significantly and positively associated with the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and overall. Given the manner in which the drug use variable was coded this means that cannabis use is associated with worse PM performance in all of the above cases. Limiting the analysis to the cannabis users within the sample, examination of the more refined measures of cannabis use set out in Table 11.4 reveals that there was a significant negative correlation between the

long-term average frequency of cannabis use and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and over the entire test-session. Thus, there is a trend for the number of short-term time-based PM errors to be increased when cannabis is used more frequently.

Cocaine

Inspection of Table 11.4 reveals that cocaine use (again defined dichotomously) was significantly and positively associated with the number of delayed recall test-sheets returned on the long-term delayed recall PM task. In the same way, cocaine use was significantly and positively associated with the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and overall. Cocaine use was associated with worse PM performance in all cases. Focusing on only the cocaine users within the sample, average long term, cocaine dose was significantly and negatively associated with the number of errors made on trial 1 of the F1 event-based PM task. However, contrary to expectation, increasing total cocaine consumption and longer durations of cocaine use were significantly associated with fewer errors on trial 3 of the F1 event-based PM task. Also contrary to expectation, total cocaine consumption was significantly and positively associated with the number of delayed recall test sheets that were returned on the long-term delayed recall PM task. Both of these findings are inconsistent with predictions and paradoxically are indicative of better performance on short-term event-based and long-term time-based PM tasks when overall cocaine consumption is increased. Nonetheless, this time in line with prediction, total cocaine consumption was significantly and negatively associated with the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session. Thus, higher lifetime cocaine consumption was related increased levels of forgetting on the Karolinska fatigue questionnaire.

As expected, the long-term average dose of cocaine per session was significantly and positively associated with the number of errors made on trial 1 of the F1 event-based PM task and negatively associated with the proportion of Karolinska fatigue questionnaires completed during the first and second halves of the test-session and overall. The long-term average frequency of cocaine use was significantly and

negatively associated with the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session. Unexpectedly, the duration of cocaine use was significantly and negatively related to the number of errors made on trial 3 of the F1 event-based PM task.

The extent to which short-term indices of ecstasy, cannabis and cocaine use were associated with performance on the F1 event-based PM task, the long-term delayed recall PM task and the Karolinska fatigue questionnaire in a sample of ecstasy/polydrug users were examined. The means and standard deviations for short-term indices of ecstasy, cannabis and cocaine use are shown in Table 11.5 and the corresponding correlations between these and the PM outcomes are presented in Table 11.6.

Table 11.5 Means and standard deviations for short-term indices of illicit drug use

	Polydrug Users		
	Mean	SD	n
Total Consumption in Last 12 Months			
Ecstasy (tablets)	26.27	63.62	87
Cannabis (joints)	267.06	767.85	112
Cocaine (lines)	60.67	133.94	79
Average Dose Per Session in Last 12 Months			
Ecstasy (tablets)	.67	1.00	87
Cannabis (joints)	1.42	2.02	112
Cocaine (lines)	2.03	3.15	79
Average Frequency of Use in Last 12 months (times per week)			
Ecstasy	.21	.44	87
Cannabis	1.04	2.02	112
Cocaine	.22	.50	79
Current Frequency of Use (times per week)			
Ecstasy	.19	.32	84
Cannabis	1.82	6.37	106
Cocaine	.38	.78	74
Weeks since last use			
Ecstasy	45.01	92.09	86
Cannabis	39.52	79.45	110
Cocaine	41.99	137.63	71

Table 11.6 Associations between short-term indices of ecstasy, cannabis and cocaine use and PM outcomes.

	Zero order correlations with:							
	F1 event-based PM task				The long-term delayed recall task	The Karolinksa fatigue PM task		
	Trial 1 errors	Trial 2 errors	Trial 3 errors	Total errors	Total number of recall tests returned	Percentage completed in first half of test-session	Percentage completed in second half of test-session	Percentage completed overall
Total Consumption in Last 12 Months								
Ecstasy (tablets)	.10	-.03	.05	.07	-.01	.03	-.09	-.02
Cannabis (joints)	-.13	.004	.02	-.08	-.12	-.09	-.12	-.13
Cocaine (lines)	.02	-.12	-.12	-.07	.12	-.26**	-.05	-.13
Average Dose Per Session in Last 12 Months								
Ecstasy (tablets)	.05	-.07	-.02	-.01	-.03	-.12	-.30**	-.25**
Cannabis (joints)	-.10	.001	.02	-.06	-.12	-.07	-.10	-.12
Cocaine (lines)	.06	-.15	-.18	-.08	-.08	-.27*	-.23*	-.28**
Average Frequency of Use in Last 12 months (times per week)								
Ecstasy	.04	-.04	.00	.01	-.04	.01	.09	-.07
Cannabis	-.15	.05	.16*	-.03	-.18*	-.10	-.14	-.15
Cocaine	-.08	-.12	.08	-.06	.24*	-.11	.16	.09
Current Frequency of Use (times per								
Ecstasy	.16	.08	.10	.13	-.03	.05	-.23*	-.13
Cannabis	-.10	-.01	-.21*	-.01	.08	.04	.09	.09
Cocaine	.15	-.08	-.13	.01	-.004	-.08	.06	-.09
Weeks since last use								
Ecstasy	.13	-.06	-.12	.02	-.03	-,08	-.10	-.11
Cannabis	-.03	-.08	-.12	-.09	-.03	-.01	.03	.05
Cocaine	.19	-.05	-.07	.06	-.11	-.02	-.05	-.09

*p<.05, **p<.01, ***p<.001, one-tailed.

Correlations between short-term indices of drug use and PM outcomes

Ecstasy

The average dose of ecstasy per session in the last 12 months and the current frequency of ecstasy use were both significantly and negatively associated with the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session. The average dose of ecstasy per session in the last 12 months showed a significant negative correlation with the proportion of Karolinska fatigue questionnaires completed over the entire test-session. Thus, higher average doses of ecstasy consumed in a typical session during the last 12 months and also increased current frequency of ecstasy use were linked to more short-term time-based PM problems.

Cannabis

The average frequency of cannabis use in the last 12 months showed a significant positive correlation with the number of errors that were made on trial 3 of the F1 event-based PM task and negatively associated with the number of delayed recall test sheets successfully returned on the long-term delayed recall PM task. Thus, increased frequency of cannabis use in the 12 months prior to the test-session was linked to worse performance on short-term event- and long-term time-based PM tasks.

Unexpectedly, the current frequency of cannabis use was also significantly and negatively associated with the number of errors made on trial 3 of the F1 event-based PM task. Thus, increased current frequency of cannabis use was related to better short-term event-based PM performance.

Cocaine

Total cocaine consumption in the last 12 months was significantly, negatively associated with the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session. This finding is in line with predictions and shows that increased cocaine consumption in the 12 months prior to the test-session was related to increased short-term time-based PM forgetting.

The average dose of cocaine per session in the last 12 months was significantly negatively associated with the proportion of Karolinska fatigue questionnaires completed during the first and second half of the test-session and also over the entire test-session. In each case, increased doses of cocaine consumed in a typical session in the 12 months prior to the test-session was related to worse short-term time-based PM performance. Increased frequency of cocaine use in the last 12 months was significantly and negatively associated with the total number of delayed recall test-sheets returned on the long-term delayed recall PM task. Increased use of cocaine was related to worse long-term time-based PM performance.

Partial correlations

Partial correlations to estimate the relationship between long-term indicators of ecstasy, cannabis and cocaine use when controlling for long-term indicators of other drug use.

In relation to ecstasy use, the association between total lifetime ecstasy consumption and the number of errors made on trial 1 of the F1 event-based PM task remained statistically significant when controlling for long-term average dose of cocaine per session, r=.25, df=62, p=.03, one-tailed. However, the relationship between the long-term average dose of ecstasy per session and the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session was no longer statistically significant when controlling for total cocaine consumption, long-term average dose of cocaine per session and the long-term average frequency of cocaine use, r=-.17, df=60, p=.10, one-tailed. Similarly, the relationships between the long-term average dose of ecstasy per session and proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and over the entire session were not statistically significant when controlling for the long-term average dose of cocaine use per session and the long-term average frequency of cannabis use, r=-.19, df=54, p=.08, one-tailed and r=-.21, df=54, p=.06, one-tailed, respectively.

With regard to cannabis use, the partial correlations between the long-term average frequency of cannabis use and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and between the long-term average frequency of cannabis use and the proportion of Karolinska fatigue questionnaires completed over the entire session were r=-.15 and r=-.14, respectively. Both partial correlations showed that

these associations were no longer statistically significant following the controls for long-term average dose of ecstasy and cocaine per session, p=.14 and p=.15, one-tailed, respectively.

In relation to cocaine use, the relationship between the long-term average dose of cocaine per session and the number of errors made on trial 1 of the F1 event-based PM task remained statistically significant following the control for total lifetime ecstasy consumption, r=.22, df=62, p=.04, one-tailed. The associations between the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session and long-term average dose of cocaine per session and the long-term average frequency of cocaine use remained statistically significant following the control for the long-term average dose of ecstasy per session, r=.23, df=62, p=.03, one-tailed and r=-.21, df=62, p=.047, one-tailed, respectively. However, the relationship between total cocaine consumption and the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session was no longer statistically significant after controlling for the long-term average dose of ecstasy per session, r=-.15, df=62, p=.25, one-tailed. The association between the long-term average dose of cocaine per session and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session fell to below statistical significance when controlling for the same long-term indices of ecstasy and cannabis use, r=-.18, df=54, p=.09. Nonetheless, following the control for the long-term average dose of ecstasy per session and the long-term average frequency of cannabis use, the association between the long-term average dose of cocaine per session and the proportion of Karolinska fatigue questionnaires completed during the entire test-session remained statistically significant, r=-.25, df=54, p=.03, one-tailed.

Partial correlations to estimate the significant associations between short-term indicators of ecstasy, cannabis and cocaine use and PM outcomes when controlling for short-term indicators of other drug use.

When controlling for the average dose of cocaine per session in the last 12 months, the associations between the average dose of ecstasy per session in the last 12 months and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and the average frequency of ecstasy use in the last 12 months and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session remained statistically significant, r=-.25, df=69, p=.02, one-tailed and r=-.24, df=66, p=.03,

one-tailed, respectively. However, the relationship between the average dose of ecstasy per session in the last 12 months and the proportion of Karolinska fatigue questionnaires completed over the entire test-session fell just short of statistical significance when controlling for the average dose of cocaine per session in the last 12 months, *r*=-.20, df=69, *p*=.05, one-tailed.

For cocaine use, the associations between a) the average dose of cocaine per session in the last 12 months and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session, *r*=-.24, df=66, *p*=.03, one-tailed, b) the average dose of cocaine per session in the last 12 months and the proportion of Karolinska fatigue questionnaires completed over the entire test-session, *r*=-.23, df=66, *p*=.03, one-tailed and c) the average frequency of cocaine use in the last 12 months and the number of delayed recall test sheets successfully returned, r=-.24, df=65, *p*=.03, one-tailed, all remained statistically significant when controlling for the current frequency of ecstasy use, the average dose of ecstasy per session in the last 12 months and the average frequency of cannabis use in the last 12 months, respectively.

Partial correlations to estimate the significant associations between short-term indicators of ecstasy, cannabis and cocaine use and PM outcomes when controlling for the effects of other short-term measures of the same drug.

For ecstasy use, the relationship between the average dose of ecstasy per session in the last 12 months and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session remained statistically significant when controlling for the current frequency of ecstasy use, *r*=-.22, df=80, *p*=.03, one-tailed. Likewise, the association between the current frequency of ecstasy use and the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session remained statistically significant after controlling for the average dose of ecstasy per session in the last 12 months, *r*=-.24, df=66, *p*=.03, one-tailed.

For cannabis use, the association between average frequency of cannabis use in the last 12 months and the number of errors made on trial 3 of the F1 event-based PM task was not significant after controlling for the current frequency of cannabis use *r*=.11, df=101, *p*=.14. However, the relationship between current frequency of cannabis use and the number

of errors made on trial 3 of the F1 event-based PM task remained statistically significant after controlling for the average frequency of cannabis use in the last 12 months, r=.17, df=101, p=.048, one-tailed.

In relation to cocaine use, the relationship between total cocaine consumption in the last 12 months and the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session was not significant after controlling for the average dose of cocaine per session in the last 12 months (r=-.08, df=75, p=.25, one-tailed). In addition, the association between the average dose of cocaine per session in the last 12 months and the proportion of Karolinksa fatigue questionnaires completed during the first half of the test-session was not significant following the control for total cocaine consumption in the last 12 months (r=-.10, df=75, p=.19, one-tailed).

Partial correlations to estimate the significant associations between long-term indicators of ecstasy and cocaine use and PM outcomes when controlling for short-term effects of drug use.

For ecstasy use, the associations between the long-term average dose of ecstasy per session and both the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session and the proportion of Karolinska fatigue questionnaires completed during the entire test-session were estimated when controlling the average dose of ecstasy per session in the last 12 months. In both cases, the association fell to a level below statistical significance, r=-.14, df=79, p=.11, one-tailed, and r=-.18, df=79, p=.06, one-tailed.

The relationships between the long-term average frequency of cocaine use and the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session and between the long-term average dose of cocaine per session and the proportion of Karolinska fatigue questionnaires completed over the entire test-session remained statistically significant when controlling for the average dose of cocaine in the last 12 months, r=-.21, df=67, p=.04, one-tailed and r=-.23, df=67, p=.02, one-tailed respectively. In addition, the relationship between total cocaine consumption and performance on the long-term delayed recall PM task remained statistically significant when controlling for the average frequency of cocaine use in the last 12 months, r=-.25, df=66, p=.02. However, the relationship between total lifetime cocaine consumption and the proportion of Karolinska fatigue questionnaires completed

during the first half of the test-session was not significant when controlling the average dose of cocaine in the last 12 months, r=-.11, df=67, p=.20.

11.4 Discussion

PM impairments in ecstasy/polydrug users have been well documented in the literature and this is a finding that has been replicated in the empirical work of this thesis. The primary aim of the current study was to examine the relationships between long- and short-term measures of ecstasy use while controlling for the effects of cannabis and cocaine use. In addition to this, the current study examined the association between PM outcomes and long-term indicators of ecstasy use whilst controlling for factors of recent ecstasy use.

Ecstasy use was linked to worse performance on all but one of the PM measures. This is a finding that is consistent with previous research (Hadjiefthyvoulou et al., 2011a; 2011b) and other empirical work in this thesis. However, the current study has furthered our understanding of ecstasy-related effects on PM and has identified clear associations between PM outcomes and a number of long-term indicators of ecstasy use. For example, total lifetime ecstasy consumption and the long-term average dose of ecstasy per session were associated with PM outcomes. Following the control for long-term indicators of other drug use and effects of recent ecstasy use, higher lifetime ecstasy consumption was linked to more event-based PM errors (F1 event-based PM task). It is possible that the regular consumption of small doses of ecstasy might cumulatively produce a neurotoxic effect which increases with lifetime use. For example, increased lifetime ecstasy consumption has been linked to structural abnormalities within the serotonergic system including degeneration of 5-HT axonal projections, abnormal regulation of 5-HT pathways and increased 5-HT_{2A} receptor levels as a neuroadaptive response to reduced serotonin activity (Di lorio et al., 2012; Fischer Hatzidimitriou, Wlos, Katz & Ricaurte 1995). Despite this evidence, increased long and short-term average doses of ecstasy per session were associated with short-term time-based PM deficits. Therefore, it might be that the consumption of larger doses of ecstasy in a typical session increases the amount of MDMA in plasma thereby enhancing neurotoxicity in the brain (Morefield et al., 2011). Larger doses of ecstasy per session have also been linked to reduced serotonergic binding in the prefrontal cortex and the hippocampus (Kish et al., 2010). In summary, the current findings point to the fact that total lifetime ecstasy consumption and the long and short-term average dose of ecstasy per session are important predictors of event- and time-based PM performance. These measures of ecstasy use may give rise to very different patterns of use and potentially point to different mechanisms of neurotoxicity..

Cannabis use was associated with poor performance on short-term event and long-term time-based PM tasks. More refined measures of cannabis use including the long-term average frequency of cannabis use were also associated with short-term time-based PM performance although this relationship was no longer significant following controls for long-term indicators of illicit drug use. Nonetheless, increased current frequency of cannabis use was associated with more short-term event-based PM errors with partial correlations showing that this effect was independent of other factors of recent use (the average frequency of cannabis use in the last 12 months).

Clearer associations were observed between factors of cocaine use and PM performance. After controlling for long-term measures of ecstasy and cannabis use and recent cocaine use, higher long-term average dose of cocaine per session was linked to worse performance on short-term event and time-based PM tasks. These findings suggest that performance on short-term event- and time-based PM tasks is sacrificed when larger doses of cocaine are consumed in a typical session. In addition, higher total cocaine consumption was linked to poorer long-term time-based PM performance. Importantly, this relationship was independent of ecstasy and cannabis use and recent cocaine use. Factors of recent cocaine use were also associated with PM performance. The average dose of cocaine per session in the last 12 months and the average frequency of cocaine use in the last 12 months were related to adverse outcomes on short- and long-term time-based PM measures, respectively. These associations remained statistically significant following controls for short-term indicators of ecstasy and cannabis use.

Previous research has also associated increased lifetime cocaine consumption with deficits in PM performance. Consistent with the findings from the current study, Hadjiefthyvoulou et al. (2011a) found that increased lifetime cocaine consumption was associated with poorer performance on the Karolinska fatigue PM task (Hadjiefthyvoulou et al., 2011a). However, the current study is the first to demonstrate a relationship between the average typical dose of cocaine per session and PM performance. PM deficits in cocaine users may in part reflect impairment of cortical and subcortical regions modulated by dopamine (Hadjiefthyvoulou et al., 2011a). In one important study, Tomasi and colleagues (2007) used functional magnetic resonance imaging to investigate brain activation during a verbal working memory task in cocaine abusers and healthy controls. Compared to controls, cocaine abusers demonstrated hypoactivation in the mesencephalon, a brain region where dopamine neurons are located. Cocaine abusers also showed larger deactivation in dopamine

projection regions (including in the putamen, anterior cingulate, parahippocampal gyrus, and amygdala) and hyperactivation in the prefrontal and parietal cortices relative to nonusers. These findings are significant given the role of the mesocortical dopaminergic system in PM processes (Goto & Grace, 2008). Importantly, Tomasi et al. (2007) found that working memory load activation was lower in the prefrontal and parietal cortices in cocaine abusers when compared with controls. This is significant since PM and EF tasks load heavily on frontal brain operations (Okuda et al., 2007; Collette et al., 2005).

Alternatively, PM deficits in cocaine users may be driven by cocaine-induced cortisol mediated hippocampal dysfunction (Fox et al., 2009; Tomasi et al., 2007; Zeigler et al., 1991). Fox et al. (2009) found elevated morning cortisol levels in cocaine-dependent participants relative to healthy controls. Enhanced cortisol levels were linked to worse learning and working memory performance on the Rey Auditory Verbal Learning Task. Increased exposure to cortisol leads to the degeneration of the hippocampus and hippocampal disinhibition (Sapolsky, Uno, Rebert & Finch, 1990; Het, Ramlow & Wolf, 2005). It might be that smaller doses of cocaine used over a prolonged period of time give rise to higher lifetime cocaine consumption resulting in elevated cortisol levels and significant degeneration of the hippocampus. On the other hand, the consumption of larger doses of cocaine per session may increase cortisol levels causing hippocampal degeneration. Hippocampal degeneration can have negative implications for PM performance given the importance of the hippocampus in checking for target stimuli (Okuda et al., 1998), retrieving the intended action associated with the target stimulus (Martins et al., 2007) and in time-based PM tasks where there is a delay between the formation of an intention and its subsequent retrieval (Adda et al., 2008). However, in relation to this proposal, it is important to note that the majority of cocaine users who were sampled also used ecstasy (and cannabis). As such the apparent cocaine-related impairments in PM might be a result of cocktail effects. For example, ecstasy use is also known to indirectly affect dopaminergic regulation through its effects on cortisol (Goto & Grace, 2008; Parrott, Lock, Conner, Kissling & Thome, 2008; Wolff et al., 2012) and so the additional effects that cocaine has on the dopaminergic systems may produce a joint effect that would not be apparent in cocaine only users.

While the current study has found a relationship between factors of ecstasy and cocaine use and laboratory-based PM performance, a number of potential limitations should be acknowledged. With respect to the inter-correlations between the PM measures, it is

noteworthy that the long-term delayed recall PM task and the Karolinska fatigue PM task were not significantly related to each other. This is somewhat surprising given that similar retrieval processes govern each task. For example, in each case, individuals must remember to perform an intended action after a specific period of time has elapsed. Despite this, the delay interval in the long-term delayed recall PM task is sufficiently longer than that in the Karolinska fatigue PM task. In consideration of this, research points towards differing processing demands of time-based PM tasks with short- and long-term delay intervals. For instance, a number of rostral prefrontal regions (right superior frontal gyrus, anterior medial frontal lobe and anterior cingulate gyrus; Okuda et al., 2002; 2007) appear to be implicated in short-term time-based PM and thus may also be involved in performance of the Karolinska fatigue PM task. By comparison, time-based PM tasks with longer delay intervals such as the long-term delayed recall PM task are suggested to load more on the left hippocampal region (Adda et al., 2008). The differing processing demands of short- and long-term PM tasks may explain why the Karolinksa fatigue PM task and the long-term delayed recall PM task were not inter-correlated.

With regard to the statistical analysis, it must be conceded that the correlations reported in Table 11.4 and Table 11.6 are unadjusted for multiple comparisons. It is important to acknowledge that with full Bonferroni correction, none of the correlations reported in Table 11.4 and Table 11.6 are significant at the adjusted alpha level. That said, each factor of illicit drug use was significantly associated with a number of PM outcomes. The situation is further complicated given that long- and short-term indices of drug use were inter-correlated with each other. In this case, it could be argued that full Bonferroni correction is too conservative and inappropriate (Sankoh et al., 1997) and there is no universally accepted method for calculating the adjusted alpha level. Despite this, some degree of correction is needed, and in these situations, an adjusted alpha level of 0.01 is sometimes adopted (e.g. Montgomery & Fisk, 2007). At this level, only 5 of the correlations between factors of drug use and the PM outcomes are statistically significant. A further method for evaluating the importance of the outcomes reported in Table 11.4 and Table 11.6 would be to use Cohen's (1988) effect size construct. This measure suggests that correlations of less than 0.1 are unlikely to represent a noteworthy effect, correlations of between 0.1 and up to 0.3 represent a small effect size, from 0.3 up to 0.5 moderate and correlations 0.5 and above a large effect size. Using this standard, only one of the correlations in Table 11.3 and Table. 11.5 which is significant at $p<0.01$, one tailed, exceed 0.3 and so would meet Cohen's criteria

for a moderate effect. However, if these criteria were adopted, the unexpected negative correlation between the long-term average frequency of ecstasy use per session and the number of errors that were made on trial 2 of the F1 event-based PM task would not be significant.

The current findings further the current understanding of how ecstasy use may affect PM performance. More refined aspects of ecstasy use including total lifetime dose, typical dose of ecstasy consumed in a single session, and the long-term frequency of ecstasy use were shown to be associated with PM. For example, larger doses of ecstasy consumed in a typical session as well as increased long-term frequency of use were associated with worse performance on short-term event- and time-based PM tasks, respectively. Factors of cocaine use were also shown to be related to PM performance. Higher total lifetime cocaine consumption and increased long-term average dose of cocaine per session were related to worse performance on a number of PM outcomes.

Chapter 12: General Discussion

12.1 Prospective memory deficits in ecstasy/polydrug users

Previous research has shown evidence of ecstasy-related impairments on both self-report (Heffernan et al., 2001a; 2001b, Montgomery & Fisk, 2007) and laboratory-based measures (Rendell et al., 2007; Rendell et al., 2009; Zakzanis et al., 2003; Hadjiefthyvoulou et al., 2011a; 2011b) of prospective memory (PM). Self-reported PM deficits in ecstasy users have been found in short-term habitual PM, long-term episodic PM and internally cued PM (Heffernan et al., 2001a; 2001b). However, due to problems with the validity of self-report measures of PM (Mäntylä, 2003; Uttl & Kibreab, 2011), recent research has tended to use laboratory-based alternatives. In the substance abuse field, some of the most frequently used laboratory-based measures of PM include the F1 event-based PM task, the long-term delayed recall PM task, the Karolinska fatigue PM task and the Cambridge PM test (CAMPROMPT). These measures have been used in previous research to show PM deficits in ecstasy/polydrug users (Hadjiefthyvoulou et al 2011a; 2011b) and were used throughout the empirical work in this thesis.

Limitations of the existing literature on prospective memory performance

One of the primary limitations of the existing literature surrounding ecstasy use and PM performance is that the majority of studies have focused on traditional indices of drug use (i.e., total lifetime exposure, number of occasions of use, duration of use and the current frequency of use). These measures are often imprecise and tell researchers relatively little about the typical consumption patterns of ecstasy users. For example, some studies that claim to have found self-reported PM deficits in ecstasy users have assessed lifetime drug use categorically whereby ecstasy users are classified according to the number of occasions of use (0, 1-9, 10-99, 100+ occasions). Assessing ecstasy use in this manner is problematic for a number of reasons. First, no information about the number of ecstasy tablets consumed is obtained. Second, those individuals that report to having used ecstasy once will be allocated to the same categorical group as those individuals who have used several times. Furthermore, based on the ordinal nature of the scale, there is a degree of inaccuracy associated with this method. Other studies have focused on the total number of tablets consumed with regard to its effect on PM performance (Bedi & Redman, 2008a; Hadjiefthyvoulou et al., 2011a; 2011b; Montgomery & Fisk, 2007). Hadjiefthyvoulou et al. (2011a; 2011b) found a clear

relationship between the total number of ecstasy tablets consumed and laboratory-based PM performance. Despite this, data relating to the lifetime consumption of ecstasy use is limited in that it tells researchers relatively little about the size of the typical dose of ecstasy per session and frequency of use. In addition, with using this method there is no way to examine individual differences in consumption patterns between different ecstasy users. For example, individuals who frequently consume a single ecstasy tablet per session will generate a similar rate of lifetime consumption compared to individuals who infrequently consume several tablets per session. Differences in the consumption patterns between ecstasy users are very important given that the size of typical dose of ecstasy per session has been linked to increased accumulation of MDMA in plasma and increased MDMA exposure in the brain (Morefield et al., 2011). The size of typical dose of ecstasy per session has also been associated with reduced serotonergic binding in PM-related brain regions including the prefrontal cortex and the hippocampus (Kish et al., 2010). In light of this evidence, it is somewhat surprising that this measure of dose has received little attention previously, especially in relation to the effects of ecstasy use on cognitive performance.

12.2 The effects of typical average dose of ecstasy per session on prospective memory performance.

The first two studies in Chapter 7 aimed to explore the effects of long- (Study 1) and short-term (Study 2) ecstasy dose per session on PM performance. It was expected that PM performance would decline when higher doses of ecstasy were consumed in a typical session. Both studies adopted a timeline technique where ecstasy users were asked to provide an indication of the size of typical dose of ecstasy per session (number of tablets consumed per session) and frequency of use (times per week). This was done for each year that ecstasy users had used ecstasy and also for each month in the 12 months prior to the test-session. These data were used to calculate long- (Study 1) and short-term (Study 2) dose of ecstasy per session. Median splits were then used to dichotomise long- and short-term ecstasy dose per session and thus create two ecstasy user groups in each case: long-term high dose ecstasy users and long-term low dose ecstasy users, short-term high dose ecstasy users and short-term low dose ecstasy users. A control group of non-ecstasy users were also included. An extensive battery of laboratory-based PM measures were administered and the extent to which long- and short-term dose of ecstasy per session can predict PM performance was examined.

Contrary to initial predictions, the findings from Chapter 7 showed that the long-term dose of ecstasy per session was not associated with event- or time-based PM outcomes. That is, long-term high dose (LTHD) ecstasy users, long-term low dose (LTLD) ecstasy users and non-ecstasy users performed comparably on the F1 event-based PM task and the long-term delayed recall task. Nonetheless, there was at least some evidence for short-term dose-related effects of ecstasy use. Higher short-term average dose of ecstasy per session (in the last 12 months) was directly related to adverse outcomes on the Karolinska fatigue PM task. Relative to short-term high dose (STHD) ecstasy users, short-term low dose (STLD) ecstasy users completed significantly more Karolinska fatigue questionnaires during the second half of the test-session. Performance on the Karolinska fatigue PM task was also worse for STHD ecstasy users relative to STLD ecstasy users. Thus, short-term time-based PM impairments were associated with higher doses of ecstasy consumed in a single session in the last 12 months.

Despite these findings, data relating to the median period of abstinence for the groups indicates that the observed short-term dose related effect might be a factor of recent ecstasy use. For example, a total of five out of the 22 STHD ecstasy users who completed the Karolinska fatigue PM task had in fact used ecstasy within the seven days prior to the test-session. This therefore raises the possibility that the observed short-term dose related effects might represent a post intoxication effect. Further analyses were computed whereby the data for these five individuals was excluded. Importantly, the same group differences on the Karolinska fatigue PM task were observed and these remained statistically significant.

What is perhaps more worrying is that individuals in the STLD ecstasy user group consumed very low doses of ecstasy per session. Some STLD ecstasy users reported that they had not consumed ecstasy in the previous 6 months with a larger group claiming to have not used ecstasy for a year or more. Without the use of objective measures of drug use (e.g., hair analyses) it is difficult to determine exactly how many STLD ecstasy users had used ecstasy recently. Nonetheless, in relation to self-reported use in the STLD ecstasy user group, ecstasy dose per session was sufficiently low enough to suggest that this group was predominantly composed of previous ecstasy users. If this data is considered alongside that for STHD ecstasy users who had generally used ecstasy more regularly in the previous 12 months, it could be suggested that the current comparison related to previous users versus current users.

With this in mind, the findings should be interpreted with caution and the acknowledgement that they may in fact relate to a short-term effect of ecstasy use on PM performance.

12.3 The effects of concurrent alcohol and ecstasy use on prospective memory performance.

One of the main limitations of the research surrounding ecstasy use and PM performance is that many ecstasy users use the drug alongside other licit and illicit substances. For example, alcohol is commonly used concurrently with ecstasy (Barrett et al., 2006; Grov, Kelly & Parsons, 2009; Fisk, Montgomery & Murphy, 2009) with research suggesting that the use of alcohol alone might give rise to PM problems (Griffiths et al., 2012; Heffernan et al., 2010). Moreover, the use of alcohol and ecstasy together has been associated with cognitive impairments (Hernandez-Rabaza et al., 2010; Vidal Infer et al., 2012) and changes in the functioning of PM-related neurotransmitters (Vidal Infer et al., 2012). This makes it difficult for researchers to determine whether apparent ecstasy-related PM deficits are attributable to the use of ecstasy, the use of alcohol, or a combination of these drugs. The purpose of Chapter 8 was to investigate the effects of long- (Study 1) and short-term (Study 2) concurrent alcohol and ecstasy use on PM performance.

Consistent with findings from Chapter 7, evidence of PM deficits were observed in Chapter 8. In Study 1, long-term high alcohol (LTHA) ecstasy users and long-term low alcohol (LTLA) ecstasy users performed worse than non-ecstasy users on a number of laboratory-based measures of event- and time-based PM. Similar findings were demonstrated in Study 2 where short-term high alcohol (STHA) and short-term low alcohol (STLA) ecstasy users performed significantly worse than non-ecstasy users on event- and time-based PM measures. These findings are largely in line with previous literature (Hadjiefthyvoulou et al., 2011a; 2011b) and provide further evidence for the detrimental effects of ecstasy use on PM performance.

Despite the apparent ecstasy-related PM deficits that were observed no effect of long- or short-term concurrent alcohol and ecstasy use was found in Chapter 8. Performance on the F1 event-based PM task, the long-term delayed recall PM task, the Karolinska fatigue PM task and the Cambridge PM test (CAMPROMPT) were similar between LTHA ecstasy users and LTLA ecstasy users and between STHA ecstasy users and STLA ecstasy users. To date, no research has examined the relationship between concurrent alcohol and ecstasy use on

cognitive performance in humans and as such it is difficult to scrutinize the current findings alongside other research. Of the evidence that is available, spatial and working memory deficits have been found in rats following the concurrent administration of alcohol and ecstasy (Hernandez-Rabaza et al., 2010). This finding is particularly important since PM performance has been linked to problems with the central executive. With this in mind, one may have expected to find concurrent alcohol and ecstasy-related effects on PM. However, this was not the case with high and low dose concurrent alcohol and ecstasy users performing similarly on all PM measures. One possible reason for the discrepancy in the findings might be linked to differences in the doses of ethanol and MDMA administered in Hernandez-Rabaza at al's study and the typical doses consumed by the concurrent alcohol and ecstasy users in Chapter 8. While, Hernandez-Rabaza and co-workers (2010) adopted a body surface area normalization method to extrapolate doses from animals to human (Reagan-Shaw et al., 2008), the authors acknowledge the difficulties associated with the translation of drug dosage from one species to another. For instance, there is a possibility that the doses of ethanol and MDMA that were administered in Hernandex-Rabaza et al's study were much larger than those typically consumed in humans thereby accounting for the cognitive impairments that were observed.

One important methodological issue that should be acknowledged relates to the way in which the high and low concurrent alcohol and ecstasy user groups were categorised. For instance, the concurrent alcohol and ecstasy user groups were dichotomised based on their alcohol use alone (i.e., For Study 1, ecstasy users who, on average, consumed more than 11.03 units of alcohol per session of ecstasy use were assigned to the LTHA ecstasy user group while ecstasy users who, on average, consumed less than 11.03 units of alcohol per session of ecstasy use were assigned to the LTLA ecstasy user group). Although no differences in PM were found between the high and low dose alcohol and ecstasy user groups, clear group differences were found between the concurrent alcohol and ecstasy user groups and non-ecstasy users. With this in mind, it is likely that the observed PM deficits are mediated by the effects of ecstasy use and not alcohol use. This finding therefore strengthens the association between ecstasy use and PM performance and suggests that the concurrent use of alcohol does not exacerbate PM impairments.

To summarise the findings, Chapter 8 showed no association between the concurrent use of alcohol and ecstasy and PM performance. However, as in Chapter 7, ecstasy-related

impairments in PM were observed. Further research is needed to fully explore the relationship between concurrent alcohol and ecstasy use on PM performance (see section 12.6)

12.4 The role of executive functioning processes in accounting for prospective memory deficits in ecstasy/polydrug users

The construct of PM is highly complex with some PM tasks requiring self-initiated, attention demanding resources that place increased load on executive functioning (EF) processes and frontal brain regions (Burgess et al., 2000; Marsh & Hicks, 1998). Furthermore, failure to plan, maintain attention, monitor the environment for cues, self-initiate a required action or to interrupt an ongoing activity implicate the prefrontal cortices and executive resources (Marsh & Hicks, 1998; McDaniel et al., 1999). As a result, it is possible that apparent PM problems might be mediated by impairments in EF.

The primary aim of Chapter 10 was to further investigate the nature of ecstasy-related deficits in PM by examining the extent to which underlying problems in executive functioning (EF) processes might underpin impairments in PM. Ecstasy users and non-ecstasy users were compared on laboratory-based measures of PM (the same measures that were administered in Chapter 8) and EF. The EF measures that were administered were chosen specifically to load on the three executive functions defined by Miyake et al. (2000). Thus, measures of updating (the computation span task), shifting (the plus/minus task and the number/letter task) and inhibition (the RLG task; repeat sequences, alphabetical sequences and the number of letters generated) were administered. The Chicago word fluency task (CWFT) was also included to measure verbal word fluency.

As in Chapter 7 and Chapter 8, clear PM impairments were observed in ecstasy users. Relative to non-ecstasy users, ecstasy users were impaired on the F1 event-based PM task, the long-term delayed recall PM task, the Karolinska fatigue PM task and the event- and time-based tasks of the CAMPROMPT (note: the CAMPROMPT was not administered in Chapter 7).

Based on the evidence from the CWFT, verbal word fluency was not impaired in

ecstasy users. Although this finding is not in line with findings from Montgomery et al. (2005b) who found that ecstasy users performed significantly worse than non-ecstasy users on the CWFT (C and S letter fluency), other research has found no evidence of verbal word fluency deficits in ecstasy users (Klugman et al., 1999; Morgan et al., 2002; Wareing et al., 2000). For example, Morgan et al. (2002) used the Controlled Oral Word Association test (Benton & Hamsher, 1976) and a category fluency task and found no evidence of ecstasy-related deficits in verbal word fluency.

In relation to Miyake et al's (2000) conceptual framework of executive functions, Chapter 10 explored updating, shifting and inhibition executive processes in ecstasy users and non-ecstasy users. Unexpectedly, both groups correctly recalled a similar number of serial positions on the computation span task. This finding is indicative of normal updating performance in ecstasy users and is inconsistent with previous research (Montgomery et al., 2005b). Montgomery and co-workers found that ecstasy users correctly recalled significantly fewer serial positions on the computation span task relative to non-ecstasy users. Similar findings were reported in a later study by Montgomery and Fisk (2008). One possible reason for the discrepancy between the findings may be related to specific characteristics of the ecstasy users in Chapter 10. Individual differences between ecstasy users across studies might help to explain these findings. Although no evidence of updating impairments were evident in ecstasy users in Chapter 10, deficits in the updating capacity are pronounced for visuo-spatial updating tasks that involve detailed processing including the recall of spatial stimuli, the recognition of figures and/or the production or reproduction of figures (Murphy et al., 2012). If this is indeed the case, it might explain why ecstasy users in Chapter 10 were unimpaired on the computation span task. For example, the computation span task loads heavily on verbal processing and involves no visuo-spatial component or recall of spatial stimulus elements. As such, it could be argued that the computation span task may not challenge the updating function sufficiently enough to identify ecstasy-related impairments. That said, this proposal should be treated with some caution given that other studies have used the computation span task and identified updating deficits in ecstasy users (Fisk & Montgomery, 2008; Montgomery et al., 2005b).

Chapter 10 found no ecstasy-related deficits in shifting processes. Although the shifting cost was lower for ecstasy users compared to non-ecstasy users on the plus/minus task, the difference between the groups was not statistically significant. Similar shifting costs

were found between ecstasy users and non-ecstasy users in the number/letter task. These findings were somewhat expected given that previous research had failed to identify ecstasy-related impairments on the plus/minus task and the number/letter task (Montgomery et al., 2005b). These findings are also in line with the conclusions from Murphy et al's critical review (Murphy et al., 2009) which suggests that the shifting component of executive functions is not adversely affected by the use of ecstasy.

Further evidence from Chapter 10 indicates that the inhibition component of executive functions is not susceptible to the effects of ecstasy use. Ecstasy users and non-ecstasy users recorded similar scores on all inhibition measures of the RLG task (repeat sequences, alphabetical sequences and the total number of letters generated). Other studies that have used the RLG task have also failed to identify impairments in inhibition in ecstasy users (Fisk & Montgomery, 2009; Fisk et al., 2004). Once again, these findings are consistent with Murphy et al's (2009) critical review which suggests that the inhibition component of EF is left unaffected by ecstasy use.

Despite finding no apparent ecstasy-related deficits on any of the EF measures, the main aim of Chapter 10 was to investigate whether PM impairments in ecstasy users were related to underlying problems in executive processes. Stepwise multiple regressions were performed for each of the PM measures (the F1 event-based PM task, the long-term delayed recall PM task and the Karolinksa fatigue PM task and the CAMPROMPT) with ecstasy use defined dichotomously (user versus nonuser) and the EF measures as potential independent variables. For all but one of the PM outcomes (i.e., errors made on trial 2 of the F1 event-based PM task), the variance accounted for by ecstasy use was largely independent of that associated with the executive function measures. Similar findings were reported by Hadjiefthyvoulou et al. (2011c). As in Chapter 10, ecstasy-related deficits were found on the F1 event-based PM task, the Karolinska fatigue PM task and the long-term delayed recall PM task. However in contrast to the findings in Chapter 10, ecstasy users in Hadjiefthyvoulou and colleagues' study reported clear impairments in EF processes. Nonetheless, ecstasy-related problems in inhibition, self-monitoring, initiation, working memory, planning, organization and task monitoring were observed although these impairments were unrelated to PM performance deficits.

The overall findings from Chapter 10 show that the ecstasy users who were tested were unimpaired on the EF measures and that for these participants Miyake et al's (2000) sub-

processes of updating, shifting and inhibition were not implicated in PM deficits. One possible explanation is that event- and time-based PM load on qualitatively different executive resources than those examined in Chapter 10. For example, the role of divided attention in PM tasks is potentially very important. To demonstrate, during the completion of event- and time-based PM tasks, individuals are required to divide their attention between ongoing task performance and remembering to retrieve a PM intention upon the presentation of a target cue, or after a period of time has elapsed, respectively. Furthermore, aspects of divided attention including controlling attention and the flow of information map onto the prefrontal cortex (Loose, Kaufmann, Auer & Lange, 2003), an area which is also implicated in PM. With this in mind, it is plausible that PM deficits in ecstasy users might be underpinned by an underlying impairment in processes facilitating divided attention. Future studies may include laboratory-based dual-task paradigms to investigate divided attention performance in ecstasy users and how this relates to performance on event- and time-based PM tasks.

12.5 The effects of long- and short-term indicators of ecstasy, cannabis and cocaine use on PM performance

Although long-term dose-related effects of ecstasy use were not established in Chapter 7, additional sampling of ecstasy/polydrug users allowed for the use of correlational analyses to systematically evaluate dose-related effects of ecstasy use on PM performance (Chapter 11). Further associations between long- (total lifetime consumption, the long-term average dose per session, the long-term average frequency of use and duration of use) and short-term (total consumption in the last 12 months, the average dose per session in the last 12 months, the average frequency of use in the last 12 months, current frequency of use and the number of weeks since last use) indicators of drug use (ecstasy, cannabis and cocaine) and PM outcomes were also examined in Chapter 11. Partial correlations were used to estimate significant associations between long-term indicators of drug use while controlling for long-term aspects of other drug use and recent use. These factors (controlling for other illicit drug use and recent use) were not considered in Chapter 7, Chapter 8 or Chapter 10 and as such were an important aspect of Chapter 11.

Consistent with the findings from Chapter 7, Chapter 8 and Chapter 10, ecstasy use was related to adverse outcomes on the F1 event-based PM task, the long-term delayed recall

PM task and the Karolinksa fatigue PM task. However in furthering the findings from these Chapters, Chapter 11 identified a number of interesting associations between PM outcomes and long-term indicators of ecstasy use. Higher lifetime ecstasy consumption was related to more event-based PM errors on the F1 event-based PM task. One crucial association which should be acknowledged is the link between higher long-term average dose of ecstasy per session and short-term time-based PM performance. Contrary to the findings of Chapter 7, larger doses of ecstasy consumed in a typical session (averaged over lifetime use) were associated with worse performance on the Karolinska fatigue PM task. Although this relationship fell just short of statistical significance following controls for the effects of other drug use and recent ecstasy use, there is at least some evidence for a dose-related effect of ecstasy use in Chapter 11. Consistent with the findings from Chapter 7, the average dose of ecstasy per session in the last 12 months was significantly associated with short-term time-based PM. More specifically, larger doses of ecstasy consumed in a typical session in the 12 months prior to the test-session were related to worse performance on the Karolinska fatigue PM task. To our knowledge, no other research has identified a relationship between the average dose of ecstasy consumed in a typical session and PM performance.

Chapter 11 found evidence of short-term event-based and long-term time-based impairments in cannabis users. These findings are consistent with previous literature which has reported cannabis-related deficits in event- and time-based PM (Hadjiefthyvoulou et al 2011a; McHale & Hunt, 2008). With regard to the long-term correlations, increased long-term average frequency of cannabis use was associated with poor performance on the Karolinska fatigue PM task although this association was not significant following controls for ecstasy and cocaine use. Increased current frequency of cannabis use was related to adverse outcomes on the Karolinska fatigue PM task indicating that cannabis-related PM deficits might be attributable to factors of recent use.

One of the key findings from Chapter 11 was the association between cocaine use and PM. Until recently, clear PM deficits had not been established in cocaine users. The first empirical study to identify PM impairments in cocaine users was carried out by Hajiefthyvoulou et al. (2011a). The authors found that larger lifetime cocaine consumption and increased frequency of cocaine use were detrimental to performance on the Rivermead Behavioural Memory test (RBMT), the Karolinska fatigue PM task and the long-term delayed recall PM task. Similar associations were found in Chapter 11. For example,

increased lifetime cocaine consumption was associated with poor short-term time-based PM performance as measured by the Karolinska fatigue PM task. Nonetheless, this relationship was no longer significant following controls for the effects of ecstasy and cannabis use. In extending the current knowledge of cocaine-related impairments in PM, Chapter 11 has identified other factors of long-term cocaine use that appear to be related to PM performance. Increased total lifetime consumption of cocaine was linked to worse long-term time-based PM performance. Larger long-term average doses of cocaine were associated with short-term event- and time-based deficits. Higher long-term average frequency of cocaine use was also linked to short-term time-based PM deficits. Recent effects of cocaine were also related to PM outcomes in Chapter 11. For instance, larger dose of cocaine per session in the last 12 months and higher average frequency of cocaine use in the last 12 months were linked to worse performance on short- and long-term time-based PM tasks, respectively. Importantly, all of the abovementioned associations were independent of the effects of ecstasy and cannabis use and recent cocaine use.

The findings from Chapter 11 are important in demonstrating how ecstasy and cocaine use might affect PM performance. In summary of the findings, total lifetime ecstasy consumption and the average dose of ecstasy consumed per session were associated with PM outcomes. Increased total lifetime ecstasy consumption was associated with poor event-based PM performance. Larger doses of ecstasy consumed in a typical session and increased long-term frequency of ecstasy use were associated with poor short-term time-based PM performance. Factors of cocaine use were also shown to be related to PM performance. Higher total lifetime cocaine consumption and increased long-term average dose of cocaine per session were related to worse performance on a number of PM outcomes. Importantly, all but one of the abovementioned associations (long-term average dose of ecstasy and short-term time-based PM performance) were independent of factors of other illicit drug use suggesting that ecstasy- and cocaine-related impairments in PM are independent from one another.

12.6 Implications and directions for future research

In light of the apparent ecstasy-related effects that have been found in this thesis, it is important to consider the neurotoxic potential of ecstasy and how this might relate to the event- and time-based PM deficits that have been observed. Considering the evidence that has been put forward in Chapter 3 concerning the neural basis of PM, two brain regions that are

clearly implicated in PM tasks include the frontopolar cortex and the hippocampus. The frontopolar cortex plays a crucial role in both event-and time-based PM tasks (e.g., Gilbert, 2011; Momennejad & Haynes, 2012; Okuda et al., 2007). For example, prefrontal areas are associated with the maintenance of an intention (Gilbert et al., 2009) and monitoring for PM targets (McDaniel & Einstein, 2011) in event-based PM tasks. In time-based PM tasks, the prefrontal cortex is implicated during the encoding of information relating to "what" an intention is "when" it should be carried out (Momennejad & Haynes, 2012). With this in mind, it is interesting to note that lower serotonin transporter densities and cortical thinning have been found in prefrontal cortex of ecstasy users (Kish et al., 2010). Thus, ecstasy-related PM impairments found in this thesis might be linked to dysfunction within this region. There is also reason to believe that PM deficits in ecstasy users are associated with abnormalities within the hippocampus. The hippocampus is important in event-based PM tasks where there is a requirement for spontaneous retrieval processes (Moscovitch, 1994), checking for a target stimulus (Okuda et al., 1998) and in retrieving the intended action associated with the target stimulus (Martins et al., 2007). The hippocampus is also crucial in time-based PM tasks where there is a delay between the formation of an intention and its subsequent retrieval (Adda et al., 2008). Significant reductions (31%) have been observed in serotonin transporter densities within the hippocampus of ecstasy users (Kish et al., 2010). It could therefore be argued that abnormalities within the hippocampus of ecstasy users mediate the event- and time-based PM deficits that have been observed. The possible role of the parietal cortex cannot be dismissed in light of research that has indicated its involvement in event- and time-based PM tasks (Benoit et al., 2012; Simons et al., 2006) and findings that have shown reduced SERT densities and cortical thinning in this region in ecstasy users (Kish et al., 2010).

Another possibility that must be considered is the potential mediating role of cortisol. By stimulating the hypothalamus-pituitary-adrenal (HPA) axis, MDMA is suggested to increase plasma concentrations of cortisol (Parrott, 2009). Parrott et al. (2008) examined salivary cortisol levels in ecstasy users and found increases of up to 800% in participants who used ecstasy when clubbing compared with baseline and dancing when drug free. More recent evidence from Wolff et al. (2012) provides further support for the importance of cortisol in relation to ecstasy-related neurotoxicity. The authors evaluated cortisol levels in ecstasy users and non-ecstasy users before and after clubbing. Compared to clubbers who had not consumed ecstasy, ecstasy-using clubbers demonstrated a 110% increase in post-clubbing

cortisol levels. Although this finding is similar to the 130% increase in post-clubbing cortisol (24 hours) levels observed in Parrott et al's (2007) study, the acute cortisol release after ecstasy use could be much larger (Parrott et al., 2013). Wolff and co-workers also noted the importance of genetically-based differences in drug metabolism in moderating the post-clubbing rise in cortisol levels. For example, post-clubbing increases in cortisol were particularly apparent in ecstasy users with the two CYP2D6 phenotypes characterised by poor or intermediate metabolism. Further genetic influences were observed whereby individuals with the COMT genotype (Met/Met) were linked to larger increases in post-clubbing cortisol. In summary, it appears that chronic exposure to MDMA could lead to dysfunction of the HPA axis especially in individuals who are genetically characterised by poor drug metabolism. Parrott, Lock, Adnum and Thome (2000) note the possible implications of elevated cortisol levels on a range of psychobiological functions including memory (Backhaus et al., 2006; Wolff et al., 2005), higher cognitive processing (McMorris et al., 2006). Indeed, it is possible that MDMA induced cortisol mediated HPA axis dysregulation might account for the PM deficits observed in ecstasy users in this thesis. For example, cortisol is implicated during the regulation of dopamine (Goto & Grace, 2008) which supports prefrontal executive processes. Chronic increases in cortisol levels have been associated with atrophy in the frontal cortex and the hippocampus, two brain regions that are implicated in PM tasks (Erickson et al., 2003).

In furthering the current understanding of PM deficits in ecstasy users, Chapter 7 and Chapter 11 highlight the importance of the typical dose of ecstasy consumed in a representative session. In Chapter 7 and Chapter 11, larger doses of ecstasy consumed per session in the 12 months prior to the test-session were associated with short-term time-based deficits in PM. In Chapter 11, a similar association was found between the long-term average dose of ecstasy consumed in a typical session (averaged over lifetime ecstasy use) and performance on the Karolinska fatigue PM task. The implications of dose per session have received little attention previously, especially in relation to cognitive performance. Rather, there has been a tendency for studies to focus on more traditional indices of drug use including total lifetime exposure, duration of use and current frequency of use. The problems associated with these measures of drug use are discussed in Chapter 7. Nonetheless, the findings from the current thesis suggest that the size of the typical dose of ecstasy per session is important and more specifically that larger doses of ecstasy consumed in a representative session give rise problems in PM performance. One possible reason for this is that that the

consumption of larger doses of ecstasy gives rise to elevated MDMA plasma concentrations that last several hours. Thus, MDMA exposure in the brain is increased and the neurotoxic effects (mentioned in the paragraphs above) are potentially exacerbated (Morefield et al., 2011). If this is the case, it is no surprise that the ecstasy users who on average consumed larger doses of ecstasy per session were impaired in PM.

The findings of dose-related impairments in ecstasy users are likely to be linked to the development of tolerance. For instance, the subjective effects of ecstasy are compromised rapidly after a period of use. As a result, many ecstasy users seek to increase their typical dose of ecstasy in order to maintain the intensity of the on-drug experience. Tolerance has been linked to serotonergic neurotoxicity (Parrott, 2005) with evidence from neuroimaging studies in ecstasy users showing reduced serotonin densities in the frontal cortex (McCann et al., 1998; Kish et al., 2010) as well as serotonin axonal damage and grey matter loss (Cowan et al., 2003; Kish et al., 2010). The concept of tolerance is based on the assumption that ecstasy use leads to the progressive degeneration of the serotonergic system. As a result, there a fewer sites for ecstasy to operate on meaning that ecstasy users need to consume higher doses of the drug to achieve the same pharmacological effect (Parrott, 2005). Some ecstasy users might even resort to periods of binging to achieve the same subjective experience. The empirical studies in Chapter 7 and Chapter 11 are the first in the field to establish a clear-relationship between average typical dose of ecstasy per session and PM performance. This finding should be used to educate ecstasy users as to the potential implications of consuming multiple ecstasy tablets in a typical session of use.

The findings from Chapter 8 showed no relationship between concurrent alcohol and ecstasy consumption and PM performance. However, relatively little research has studied this relationship in humans. In fact, the research presented in Chapter 8 was the first in the field to study the effect of concurrent alcohol and ecstasy use on any aspect of cognitive performance. Clearly, further research is needed to fully explore the effect of concurrent alcohol and ecstasy consumption on cognitive functions other than PM. However, the relationship between concurrent alcohol and ecstasy consumption and PM performance also warrants further investigation. Access to a larger sample of concurrent alcohol and ecstasy users would allow for the use of correlational analyses to explore the relationships between the size of typical dose of alcohol per session of ecstasy use and PM performance measures. This might be a more powerful technique compared to simply categorising concurrent alcohol

and ecstasy users on the basis of a median split. As mentioned previously, median splits often lack precision and are associated with loss of statistical power (Federov et al., 2009). Thus, future research should focus on obtaining larger samples through which to the effects of concurrent alcohol and ecstasy use on PM performance can be more effectively studied using correlational analysis.

Should a relationship be established between concurrent alcohol and ecstasy use and PM performance, it would be useful to examine the potential mechanisms that might underpin this association. Animal research has linked concurrent alcohol use to neuronal depletion and reactive microgliosis in the dentate gyrus region of the hippocampus (Hernandez-Rabaza et al., 2010). While this might also be the case in humans, it might also be interesting to investigate the potential mediating role of other factors such as cortisol. For instance, the consumption of alcohol and ecstasy together might further stimulate the HPA axis thereby increasing plasma concentrations of cortisol to levels above those associated with ecstasy use alone. On the basis of Parrott et al's (2008) study, researchers could examine salivary cortisol levels pre-clubbing, during-clubbing and post-clubbing in individuals who consume either, alcohol and ecstasy together, ecstasy alone, alcohol alone or in those who do not consume any drugs. Acute (on-drug) or post-clubbing (24 h, 48 h) increases in cortisol levels in the concurrent alcohol and ecstasy user group relative to the ecstasy user group might be indicative of an alcohol and MDMA induced, cortisol mediated HPA axis dysregulation. As mentioned previously, cortisol has important implications for PM performance. For example, it is involved in the regulation of dopamine (Goto & Grace, 2008), which is important for prefrontal executive processes including PM.

The scope for further research into the effects of ecstasy use on PM performance has been touched upon in the above paragraphs. However, further studies are needed to identify the specific mechanisms that drive PM-related impairments in ecstasy users. More specifically, it is important to determine what makes ecstasy users who consume high doses of ecstasy per session more susceptible to PM deficits. The use of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) would allow for researchers to examine regional brain activation is ecstasy users during the completion of PM tasks. The nature of any PM performance deficits could be explored alongside the neuroimaging data in order to identify whether there are any clear differences in brain activation. The inclusion event-related potentials (ERP) and Magnetoencephalography (MEG) alongside fMRI would

be useful given that these techniques are especially accurate in relation to the time-course of cognitive processing. Used together, these techniques would also provide detailed information relating to the exact sequence of processes within spatially defined neural networks (Dale et al., 2000).

The overall evidence presented in Chapter 7, Chapter 8, Chapter 10 and Chapter 11 is indicative of clear ecstasy-related impairments in PM. The implications of PM deficits give reason for serious concern and should not be ignored. Each day, people are confronted with a range of important versus unimportant PM tasks and in some cases, failure to carry out an intended action can severely impact everyday functioning. For example, failing to remember to attend a medical appointment or a business meeting could potentially have severe consequences. The PM deficits noted in this thesis and in particular the relationship between average dose of ecstasy per session and PM outcomes should be used to educate users as to the potential dangers of ecstasy use.

12.7 Limitations

A number of general limitations must be considered in relation to the empirical work reported in this thesis (in addition to those noted in the empirical chapters). One issue concerns the purity of the ecstasy tablets consumed by the ecstasy user groups. More specifically, relatively little is known about the pharmacological constituents of the ecstasy tablets and in particular their MDMA content. An important review by Parrott (2004) investigated the extent to which tablets that were assumed to be "ecstasy" actually contained MDMA. Data from surveys into the pharmacological constituents of ecstasy tablets, reported doses and empirical reports of perceived purity were reviewed. In the mid 1990's and up until the late 1990's, "ecstasy" tablets contained high quantities of substances other than MDMA including 3,4methylenedioxyethylamphetamine (MDEA) and 3,4, methylenedioxyamphetamine (MDA). However, at the present time, it appears that "ecstasy" tablets typically consumed by ecstasy users do contain high proportions of MDMA (Ramsey, 2003). Further evidence for this proposal is derived from Morefield et al. (2011) who found that the majority of "ecstasy" tablets consumed by ecstasy users contained pure MDMA while others contained high proportions of MDMA with lower proportions of MDEA, MDA and other substances. Although the "ecstasy" tablets consumed by the ecstasy users who participated in the present

empirical work were not analysed for their substance content, it is reasonable to assume that the “ecstasy” tablets consumed did in fact contain high quantities of MDMA.

As is the case with much of the existing literature, the empirical work in this thesis is based on self-report data in relation to drug use. Alternative, objective measures of drug use including hair and urine samples were taken from participants in all studies of this thesis. However, due to a lack of technical staff and analysis equipment, analyses have not yet been performed. Nonetheless, there is a high degree of concordance between self-report and objective measures of recent drug use with the majority of substance users accurately reporting their drug use. For example, urine sampling techniques have been used to confirm self-reported recent drug use (McGregor & Makkai, 2003) while hair sampling techniques have been used to confirm the accuracy of longer term drug use estimates (Vignali, Stramesi, Vecchio & Groppi, 2012) thus demonstrating high levels of concordance between short-and long-term objective measures of drug use and self-reported drug use. Importantly, concordance between self-reports and objective measures of drug use has been demonstrated for the major illicit recreational drugs [e.g., ecstasy (Scholey et al., 2011; Yacoubian & Wish, 2006), cannabis and cocaine (Vignali et al., 2012; Zaldívar et al., 2009)].

In relation to the empirical work presented in Chapter 7, Chapter 8 and Chapter 10, the ecstasy user groups were characterised primarily by their ecstasy use and also the use of other licit and illicit substances. Thus, it is feasible that the observed PM deficits in these chapters are attributable to other drugs known to affect PM performance such as alcohol, tobacco, cannabis or cocaine. In addition, it is possible that the concurrent use of ecstasy and any one or combination of other drugs may explain some of the PM deficits that were observed in ecstasy users. The possibility that concurrent alcohol and ecstasy use may intensify PM deficits in ecstasy users was not supported in the empirical work outlined in Chapter 8. In Chapter 11, correlation analyses were adopted to examine the relationships between long- and short-term indicators of ecstasy use and PM performance. For significant relationships, partial correlations were then used to control for the effects of cannabis and cocaine and aspects of recent use. Significant evidence was found for an association between ecstasy use and PM performance with partial correlations showing that this relationship was independent of factors of cannabis and cocaine use and aspects of recent ecstasy use.

12.8 Overall summary

The evidence presented in Chapter 7, Chapter 8, Chapter 10 and Chapter 11 provides strong evidence for PM impairments in ecstasy users. To an extent, these ecstasy-related deficits appear to be independent of the effects of other illicit drugs including cannabis and cocaine (Chapter 11). In Chapter 7, an association was found between the average dose of ecstasy consumed in a typical session in the last 12 months and short-term time-based PM performance. Larger doses of ecstasy consumed in the 12 months prior to the test-session were related to increased time-based PM impairments on the Karolinska fatigue PM task. This finding was replicated in Chapter 11. Findings from Chapter 8 failed to demonstrate an affect of concurrent alcohol and ecstasy use on PM performance. No EF deficits were found in ecstasy users in Chapter 10. Ecstasy-related deficits in PM were found to be unrelated to problems in verbal word fluency, updating, shifting and inhibition. Chapter 11 identified refined and specific indicators of ecstasy and cocaine use that predict PM performance. Total lifetime ecstasy and cocaine consumption and the long-term average dose of ecstasy and cocaine per session were related to worse performance on PM tasks. The findings presented in this thesis emphasize the need for researchers to focus more directly on the average dose of ecstasy and cocaine per session alongside the more traditional measures such as total lifetime dose and frequency of use when investigating cognitive performance in drug users.

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Appendix 1

Background drug use questionnaire (Montgomery et al., 2005)

Participant Number _____

Height _____

Weight _____

Gender _____

Age _____

1. Have you ever used the drug ecstasy? Yes/No*

(If you answered "No", please move on to Question 16)

2. How long have you been taking ecstasy? Months _____ Years _____

3. How aware are you that using the drug ecstasy may have harmful long-term effects on your health?

(*Please tick relevant answer*)

Very aware ____

Quite aware ____

Unsure ____

Quite unaware ____

Very unaware ____

Can you explain below what these harmful effects may be?

4. Are you concerned about the possible dangers of using ecstasy?

(*Please tick relevant answer)*

Extremely Concerned ____

Very Concerned ____

Concerned ____

Slightly Concerned ____

Not Concerned ____

5. How do you find out information about ecstasy?

(Please tick all relevant answers)

TV-News		Radio	
TV-Specialist Programmes \Debate		Drug Agencies	
Daily Newspaper		Drug Leaflets	
Music Magazines		Friends	
Magazine		Clubs	
Other			

6. Where do you usually take ecstasy?
(Please tick relevant boxes)

Pubs/Bars	
Night-clubs	
Rave Events	
Private House/Flat	
Parties	
Own Home	
Friends Home	
Other	

7. What activities do you participate in when under the influence of ecstasy?
(Please tick relevant boxes)

Dancing	
Listen to Music	
Talking	
Driving	
Sexual Behaviour	
Drinking	
Smoking	
Other	

8. Do you take any sort of precautions when using ecstasy? Yes\No

(E.G. Vitamins)

*If **yes** please give details*

9. Are you aware that medical advice suggests that Yes___ No ____

you should take precautions when using ecstasy?

*If **yes** can you explain below what precautions should be taken and why*

10. When under the influence of ecstasy:

(a) Do you take regular rest-breaks when dancing Yes--- No---

(b) Do you monitor your fluid intake Yes--- No---

(c) Is there anything else you do Yes--- No---

*If **yes** please give details*

11. Is there a maximum number of ecstasy tablets you will take in one session? Yes--- No---

If **Yes**, what is the maximum number _____

12. What factors decide when you have taken enough ecstasy tablets in one session? **(*Please give details below*)**

.....
.....

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

.....
.....

.....
.....

13. Do you believe that since using ecstasy you have changed in any way?

Please look at the following list very carefully

(For example, if you believe that since using ecstasy you have become more caring then tick caring under the heading MORE. If however you feel that you have become less caring then tick caring under the heading LESS. If you feel that you have not become any more or less caring the tick caring under the heading NO CHANGE)

	MUCH MORE	**MORE**	**NO CHANGE**	**LESS**	**MUCH LESS**
CARING					
PARANOID					
ALERT					
DEPRESSED					
SOCIABLE					
AGGRESSIVE					
HAPPY					
HEALTHY					
MOODY					
PATIENT					
IRRITABLE					
CONFIDENT					
SAD					
LOVING					

CONFUSED					

Any other changes _____

---

14. What has stopped you taking ecstasy in the past?

(Please tick relevant boxes)

Bad Experience (You)	
Bad Experience (Other)	
Work/College	

Parents	
Short Term Health (Physical)	
Long Term Health (Physical)	
Death	
Responsibilities	
Prison	
Psychological Problems (Short Term - in the last 1 month)	
Anxiety	
Depression	
Flashbacks	
Panic Attacks	
Paranoia	
Psychological Problems (Long Term - continuing after 1 month)	
Anxiety	

Depression	
Flashbacks	
Panic Attacks	
Paranoia	
Other (please specify)	

15. From the following list, please indicate what type of other drugs you use **at the same time** as ecstasy and the frequency of use.

(Please tick all relevant boxes)

Drug	**Always**	**Frequently**	**Occasionally**	**Never**
Alcohol				
Amphetamine				
Cannabis				
Cocaine				
Crack				
DMT				

GHB				
Herbal E				
Heroin				
Ketamine				
LSD (Acid\Blotters)				
LCB				
Mushrooms				
Poppers				
Prozac				
Salvia Divindrum				
Tranquillisers				
Tobacco				
Viagra				
Steroids				
Mephedrone (Meow)				
Naphyrone				

Other				

16. From the following list, please indicate what type of other drugs you **have used in the last three months** use and the frequency of use.

(Please tick all relevant boxes)

Drug	**Always**	**Frequently**	**Occasionally**	**Never**
Alcohol				
Amphetamine				
Cannabis				
Cocaine				
Crack				
DMT				
GHB				
Herbal E				
Heroin				
Ketamine				
LSD				

(Acid\Blotters)				
LCB				
Mushrooms				
Poppers				
Prozac				
Salvia Divindrum				
Tranquillisers				
Tobacco				
Viagra				
Steroids				
Mephedrone (Meow)				
Naphyrone				
Other				

17. From the following list, please indicate which types of drugs you have used in the past. Please indicate when you **first began using** and when you **last used** the drug.

If less than a day, indicate hours previous

Drug	**When did you first use?**	**When did you last use? (Please circle one only)**

	mm/yr.	**Hours Previous**	**Days Previous**	**Weeks Previous**	**Months Previous**	**Years Previous**
Ecstasy (MDMA)			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Alcohol			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Amphetamine			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Cannabis			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Cocaine			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Crack			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
DMT			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
GHB			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Herbal E			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Heroin			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Ketamine			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10	1 2 3 4 5 6 7 8 9 10

					11	
LSD (Acid\Blotters)			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
LCB			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Mushrooms			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Poppers			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Prozac			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Salvia Divindrum			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Tranquillisers			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Tobacco			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Viagra			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Steroids			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10	1 2 3 4 5 6 7 8

					11	9 10
Mephedrone (Meow)			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 67 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Naphyrone			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Other			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10

18. Please list any controlled substances, prescription medications, and alcohol you have consumed **in the last 10 days?** Please list ALL occasions during the last 10 days.

Substance	**Form, e.g., skunk, rocky, tablets, powder**	**Days/ hours previous**	**Amount taken**			
			Grams Dose	**Cost** *e.g. bags/wraps*		**Units** *e.g. joints, line*

19a) How would you describe you current pattern of **ECSTASY** use?

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking ecstasy
- Select an average month of use within that year
- Estimate the total number of ecstasy tablets you would normally have taken during one session
- Indicate frequency of use, e.g., number of times per week/month/year

Continue to fill in each consecutive year regardless of whether you used ecstasy or not.

If you have not used for a particular year, continue to enter the year and specify a month, and then enter zero in the space provided for the total number of tablets taken.

YEAR (Fill in for each year from the first year that you started using the drug.	MONTH	Total number of tablets taken in one session	Frequency of Use	Route of Administration	Typical alcohol consumption per session of ecstasy use (units)
e.g. 1993	***e.g., June***	***e.g., 1***	***e.g., Once a Week/ Twice a year***	***e.g., Tablet/Swallow***	***e.g., 10 units per occasion***

This year	Last 30 days		How many times?		

19b).Did you consistently use at this rate for each month in that year?

Yes/ No

19c). For the last 12 months, please estimate your pattern of ecstasy use for each month.

Estimate the total number of ecstasy tablets and the frequency of use for each month

Month	**Total amount taken in one session (tablets/grams/mg)**	**Frequency of use**	**Route of Administration**
Current Month-1	1 tablet	Once during this month	Swallow
Current Month-2			
Current Month-3			
Current Month-4			
Current Month-5			
Current Month-6			
Current Month-7			
Current Month-8			
Current Month-9			
Current Month-10			
Current Month-11			

20a). How would you describe you current pattern of **KETAMINE** use?

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

*In what form do you take **Ketamine**?*

Powder _____
Tablets (please indicate type) _____

Other _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking ketamine
- Select an average month of use within that year
- Estimate the total amount you would normally have taken during one session (please specify the form of the dose, i.e tablet, powder, etc)
- Indicate frequency of use, e.g., number of times per week/month/year

YEAR (Fill in for each year from the first year that you started using the drug.	MONTH	Total grams in one session (1 gram is typically 10 lines)	Frequency of Use	Route of Administration	Total alcohol consumption when using ketamine (units)
e.g. 1993	***e.g., June***	***e.g., 1 gram =10 lines / 0.1 gram=***	***e.g., Once a Week/ Twice a year***	***e.g., Powder***	***e.g., 10 units per occasion***

		1 line			
This year	Last 30 days		How many times?		

20b). Did you consistently use at this rate for each month in that year?

Yes/ No (If you answered No, please answer Question 20c).

20c). For the last 12 months, please estimate your pattern of ketamine use for each month.

Month	**Total amount taken in one session (tablets/grams/mg)**	**Frequency of use**	**Route of Administration**
Current Month-1	1 tablet	Once during this month	Swallow
Current Month-2			
Current Month-3			
Current Month-4			
Current Month-5			
Current Month-6			
Current Month-7			
Current Month-8			
Current Month-9			
Current Month-10			
Current Month-11			

21a) How would you describe you current pattern of **CANNABIS** use?

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ Previous user (more than 6 months since last used)

*In what form do you take **Cannabis**?*

Joints _____

Other _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking Cannabis
- Select an average month of use within that year
- Estimate the total number of joints you would normally have taken during one session

- Indicate frequency of use, e.g., number of times per week/month/year

YEAR (Fill in for each year from the first year that you started using the drug.	MONTH	Total number of joints taken in one session	Frequency of Use	Route of Administration	Total alcohol consumption when using cannabis (units)
e.g. 1993	***e.g., June***	***e.g., 1 joint***	***e.g., Once a Week/ Twice a year***	***e.g., smoke***	***e.g., 10 units per occasion***
This year	Last 30 days		How many times?		

21b) Did you consistently use at this rate for each month in that year?

Yes/ No (If you answered No, please answer Question 21c).

21c). For the last 12 months, please estimate your pattern of cannabis use for each month.

Month	**Total amount taken in one session (tablets/grams/mg)**	**Frequency of use**	**Route of Administration**
Current Month-1	1 tablet	Once during this month	Swallow
Current Month-2			
Current Month-3			
Current Month-4			
Current Month-5			
Current Month-6			
Current Month-7			
Current Month-8			
Current Month-9			
Current Month-10			
Current Month-11			

22a) Please estimate your pattern of **COCAINE** use from the first year of taking the drug to present use.

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

---

*In what form do you take **cocaine**?* _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking the drug
- Select an average month of use within that year
- Estimate the total amount you would normally have taken during one session

- Indicate frequency of use, e.g., number of times per week/month/year

YEAR (Fill in for each year from the first year that you started using the drug.	MONTH	Total number of lines taken in one session	Frequency of Use	Route of Administration	Total alcohol use when using cocaine (units)
e.g. 1993	***e.g., June***	***e.g., 1***	***e.g., One a Week/ Twice a year***	***e.g., Powder, Snort***	***e.g., 10 units per occasion***

This year	Last 30 days		How many times?		

22b) Did you consistently use at this rate for each month in that year?

Yes/No (If you answered No, please answer Question 22c).

22c) For the last 12 months, please estimate your pattern of use for this drug for each month.

Month	**Total amount taken in one session (tablets/grams/mg)**	**Frequency of use**	**Route of Administration**
Current Month-1	1 tablet	Once during this month	Swallow
Current Month-2			
Current Month-3			
Current Month-4			
Current Month-5			
Current Month-6			
Current Month-7			
Current Month-8			
Current Month-9			
Current Month-10			
Current Month-11			

23a). **Other drug regularly used:** Please estimate your pattern of use from the first year of taking the drug to present use. **These may also include drugs that have been previously termed "legal highs" i.e meow (mephedrone), naphyrone, etc**

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

Which Drug? _____

In what form? _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking the drug
- Select an average month of use within that year
- Estimate the total amount you would normally have taken during one session
- Indicate frequency of use, e.g., number of times per week/month/year

YEAR (Fill in for each year from the first year that you started using the drug.	MONTH	Total dose per occasion	Frequency of Use	Route of Administration	Typical alcohol use when using the drug (units)
e.g. 1993	***e.g., June***	***e.g., 1 gram***	***e.g., One a Week/ Twice a year***	***e.g., powder/snort***	***e.g., 10 units per occasion***

This year	Last 30 days		How many times?		

23b) Did you consistently use at this rate for each month in that year?

Yes/ No (If you answered No, please answer Question 23c).

23c) For the last 12 months, please estimate your pattern of use for this drug for each month.

Month	**Total amount taken in one session (tablets/grams/mg)**	**Frequency of use**	**Route of Administration**
Current Month-1	1 tablet	Once during this month	Swallow
Current Month-2			
Current Month-3			
Current Month-4			
Current Month-5			
Current Month-6			
Current Month-7			
Current Month-8			
Current Month-9			
Current Month-10			
Current Month-11			

24a). **Other drug regularly used:** Please estimate your pattern of use from the first year of taking the drug to present use. **These may also include drugs that have been previously termed "legal highs" i.e meow (mephedrone), naphyrone, etc**

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

Which Drug? _____

In what form? _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking the drug
- Select an average month of use within that year
- Estimate the total amount you would normally have taken during one session

- Indicate frequency of use, e.g., number of times per week/month/year

e.g. Year 1 1993	June	e.g. 1	One a Week	e.g. Smoke, Swallow, Inject, Snort	

This year	Last 30 days		How many times?		

24b) Did you consistently use at this rate for each month in that year?

Yes/ No (If you answered No, please answer Question 24c).24c) For the last 12 months, please estimate your pattern of use for this drug for each month.

Month	Total amount taken in one session (tablets/grams/mg)	Frequency of use	Route of Administration

25. How many years of full time education have you completed from primary school to date?

_____Years

26. From the following list, please indicate if you have obtained any of the following educational qualifications?

Qualification	**Y\N**	**Details**
CSE		
GCE		
GCSE		
A LEVEL		
NVQ		
GOV. EMPLOYMENT TRAINING SCHEME		
CRAFT\TRADE (EG CITY & GUILD)		
HND		
DEGREE		

OTHER		
NONE		

27. Do you have any convictions for drugs Yes--- No---

*If **yes**, would you please give details below?*

E.g. year of conviction, type of drug, type of offence

28. Do you have any other convictions Yes--- No---

*If **yes**, would you please give detail below?*

E.g. year of conviction, type of offence

29. What are your current living circumstances?

(Please tick relevant box)

Live Alone	
Parental Home	
Live with partner	
Marriage Partner	
Single Parent Family	
Live with Friends	
No Fixed Abode	
Other	

30. On Average approximately how much alcohol do you normally consume?

(E.g. 1 unit = 1 glass of wine; 1 measure of spirit pint of beer)

Daily	
Weekly	
Fortnightly	
Monthly	
Other	

31. Have you ever experienced or been hospitalised for any of the following conditions?

- Neurological *Yes/No
- Heart *Yes/No
- Respiratory *Yes/No

If **yes, can you please explain what they were.*

32. Have you ever been diagnosed as suffering from any of the following conditions?

- Diabetes *Yes/No
- Anxiety *Yes/No
- Depression *Yes/No
- Flashbacks *Yes/No
- Panic Attacks *Yes/No
- Paranoia *Yes/No
- Phobias *Yes/No
- Schizophrenia *Yes/No

If **yes, did you receive treatment? - Please give detail*

33. Are you currently taking any prescription drugs *Yes/No

*If yes, please give the name of the drug _____

34. Do you consider yourself to be in good health?

(Please tick relevant box)

Very Good	
Good	
Average	
Poor	
Very Poor	

35. What is your current employment status?

(Please tick relevant box)

Employed full-time	
Employed part-time	
Unemployed	
Self-employed	
Student	
Other. e.g. Sick, Disabled, Homemaker	

Appendix 2

Epworth Sleepiness Scale (Johns, 1991)

PARTICIPANT NUMBER

DATE _____ TIME _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose *the most appropriate number* for each situation.

0 = Would *never* doze off

1 = *Slight* chance of dozing

2 = *Moderate* chance of dozing

3 = *High* chance of dozing

SITAUTION	CHANCE OF DOZING
Sitting and reading	———
Watching TV	———
Sitting, inactive, in a public place (e.g., a theatre or a meeting)	———
As a passenger in a car for 1 hour without a break	———
Lying down to rest in the afternoon when circumstances permit	———
Sitting and talking to someone	———
Sitting quietly after lunch without alcohol	———
In a car, while stopped for a few minutes in the traffic	———

Appendix 3

Appendix relating to inferential statistics not reported in Chapter 7

Study 1

Demographical data for long-term high dose (LTHD) ecstasy users, long-term low dose ecstasy users (LTLD) and non-ecstasy users (Study 1).

One-way ANOVA revealed that there was a significant age difference between the LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users, $F(2, 89)=8.75$, $p<.001$. Tukey's post hoc test showed that non-ecstasy users ($M=20.92$, $SD=2.22$) were significantly younger than LTLD ecstasy users ($M=23.52$, $SD=7.20$), $p<.001$. There was no significant difference in age between non-ecstasy users and LTHD ecstasy users ($M=21.91$, $SD=2.11$), $p=.21$. The age difference between LTHD ecstasy users and LTLD ecstasy users did approach statistical significance, $p=.07$, such that LTHD ecstasy users were younger than LTLD ecstasy users.

One-way ANOVA revealed a significant difference between the groups in terms of years of education, $F(2, 88)=3.40$, $p=.04$. Tukey's post hoc test showed that non-ecstasy users ($M=16.15$, $SD=2.00$) had studied for a significantly shorter period of time compared to LTLD ecstasy users ($M=17.45$, $SD=1.99$), $p=.04$. The difference in years of education between LTHD ecstasy users ($M=16.22$, $SD=1.78$) and LTLD ecstasy users approached statistical significance, $p=.10$. The number of years of education completed by non-ecstasy users and LTHD ecstasy users did not differ significantly, $p=.99$.

A series of one-way ANOVAs revealed that the groups did not differ significantly in terms of intelligence (Raven's Progressive Matrices) $F(2, 85)=.30$, $p=.75$, cigarette consumption, $F(2, 27)=.58$, $p=.57$, alcohol consumption, $F(2, 83)=.71$, $p=.50$, Epworth Sleepiness Scale score, $F(2, 98)=1.39$, $p=.25$, arousal, $F(2, 84)=.52$, $p=.60$, anxiety, $F(2, 83)=.05$, $p=.96$ and depression, $F(2, 84)=.50$, $p=.61$.

Background drug use data for LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users (Study 1).

The medians shown in Table. 7.2 indicate that LTLD ecstasy users consumed more cannabis over their lifetime relative to LTHD ecstasy users and non-ecstasy users. LTHD ecstasy users consumed more cannabis over their lifetime relative to non-ecstasy users. Kruskal-Wallis tests revealed that there was a significant difference between LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users in terms of total lifetime consumption of cannabis, $\chi^2(2)=14.34$, $p<.001$, Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) showed that LTLD ecstasy users had consumed significantly more cannabis over their lifetime compared to non-ecstasy users, U=64.50, $p<.001$. No significant differences were found between LTHD ecstasy users and non-ecstasy users, U=94.50, $p=.06$, or LTHD ecstasy users and LTLD ecstasy users, U=146.00, $p=.45$ in terms of total lifetime consumption of cannabis. The median data shows that LTHD ecstasy users consumed more cocaine over their lifetime compared to LTLD ecstasy users with Mann-Whitney U test showing that the difference was not statistically significant, U=87.00, $p=.39$.

Averaged across lifetime use, LTLD ecstasy users used higher doses of cannabis per session compared to LTHD ecstasy users and non-ecstasy users. The long-term average dose of cannabis use per session was higher for LTHD ecstasy users compared to non-ecstasy users. Kruskal-Wallis tests revealed that there was a significant difference between the groups in long-term average dose of cannabis use, $\chi^2(2)=6.29$, $p=.04$. However, there was no significant difference in the long term average dose of cannabis use between non-ecstasy users and LTHD ecstasy users, U=93.00, $p=.03$, non-ecstasy users and LTLD ecstasy users, U=95.00, $p=.03$ or LTHD ecstasy users and LTLD ecstasy users, U=157.00, $p=.89$.

The median data indicates that the duration of cannabis use as higher for LTLD ecstasy users compared to LTHD ecstasy users and non-ecstasy users. LTHD ecstasy users had been using cannabis for longer than non-ecstasy users. Kruskal-Wallis tests revealed that there was a significant difference between the groups in terms of their duration of cannabis use, $\chi^2(2)=12.18$, $p=.002$, Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) showed that LTLD ecstasy users had used cannabis for a significantly longer duration of time compared to non-ecstasy users, U=75.00, $p=.001$. There was no significant difference in the total duration of cannabis use between LTHD ecstasy users and non-ecstasy users, U=138.50, $p=.04$, or LTHD ecstasy users and LTLD ecstasy

users, U=124.00, *p*=.10. The median data shows that LTLD ecstasy users had been using cocaine for longer than LTHD ecstasy users. The group comparison was not significant, U=95.50, *p*=.60.

The median data shows that LTHD ecstasy users used cannabis more frequently over their lifetime than LTLD ecstasy users and non-ecstasy users. LTLD ecstasy users used cannabis more frequently over their lifetime compared to non-ecstasy users. Kruskal-Wallis tests revealed that there was a significant difference between the groups in terms of their long-term frequency of cannabis use, $\chi^2(2)=6.28$, *p*=.04. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) showed that there was no significant difference in the long-term frequency of cannabis use between LTHD ecstasy users and non-ecstasy users, U=85.00, *p*=.02, or LTLD ecstasy users and nonusers, U=105.50, *p*=.07. Nonetheless, it is noteworthy that the differences between these groups did approach statistical significance. LTHD ecstasy users and LTLD ecstasy users did not differ significantly in terms of their long-term frequency of cannabis use, U=147.50, *p*=.65. The median data shows that that the long-term average frequency of cocaine use was higher for LTLD ecstasy users compared to LTHD ecstasy users with Mann-Whitney U test revealing that the group difference was not statistically significant, U=113.50, *p*=.98.

With regard to period of abstinence, the median data shows that LTHD ecstasy users had used ecstasy more recently than LTLD ecstasy users. Mann-Whitney U test revealed that there was no significant difference between LTHD ecstasy users, LTLD ecstasy users and non-ecstasy users in terms of the number of weeks since ecstasy was last used, U=216.00, p=.73. The median data indicates that LTLD ecstasy users had used cannabis more recently than LTHD ecstasy users and non-ecstasy users. LTHD ecstasy users had used cannabis more recently than non-ecstasy users. Despite, this there Kruskal-Wallis test revealed that there was no significant difference between the groups, $\chi^2(2)=4.37$, *p*=.11. The median data shows LTHD ecstasy users had used cocaine more recently than LTLD ecstasy users with Mann-Whitney U test showing that the difference was not statistically significant, U=82.50, *p*=.15.

For descriptive data relating long-term background drug use variables, see Chapter 7, Table 7.2.

Study 2

Demographical data for short-term high dose (STHD) ecstasy users, short-term low dose (STLD) ecstasy users and non-ecstasy users (Study 2).

One-way ANOVA showed that there was a significant age difference between STHD ecstasy users, STLD ecstasy users and non-ecstasy users, F(2, 89)=5.03, *p*=.008. Tukey's post hoc test showed that non-ecstasy users (M=20.92, SD=2.22) were significantly younger than STHD ecstasy users (M=22.48, SD=2.94), *p*=.04, and STLD ecstasy users (M=22.52, SD=2.27), *p*=.03. There was no significant difference in age between short-term high-dose ecstasy users and short-term low-dose ecstasy users, *p*=.99. A series of one-way ANOVAs revealed no significant differences between the groups in terms of intelligence (Raven's Progressive Matrices), F(2, 87)=.398, *p*=.38 , years of education, F(2, 90)=.95, *p*=.39, cigarette consumption, F(2, 28)=.30, *p*=.74, alcohol consumption F(2, 85)=1.10, *p*=.34, Epworth Sleepiness Scale Score F(2, 90)=.95, *p*=.39, arousal, F(2, 86)=1.61, *p*=.21, anxiety, F(2, 85)=.01, *p*=1.00 and depression, F(2, 86)=.07, *p*=.94.

Background drug use data for STHD ecstasy users, STLD ecstasy users (STLD) and non-ecstasy users (Study 2).

The median data in Table 7.6 indicates that STHD ecstasy users consumed more cannabis in the previous 12 months compared to both STLD ecstasy users and non-ecstasy users. STLD ecstasy users consumed more cannabis in the previous 12 months relative to non-ecstasy users. Kruskal-Wallis test showed that the overall group difference was significant, $\chi^2(2)=8.71$, *p*=.01. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) revealed that STHD cannabis users consumed significantly more cannabis in the previous 12 months compared to non-ecstasy users, U=125.50, *p*=.005. The difference between STHD ecstasy users and STLD ecstasy users was not significant, U=139.50, *p*=.06. No significant difference was found between STLD ecstasy users and non-ecstasy users, U=180.00, *p*=.21. The median data indicates that STHD ecstasy users consumed more cocaine in the previous 12 months compared to STLD ecstasy users with Mann-Whitney U test revealing that the difference was statistically significant, U=129.00, *p*=.50.

The median data shows that the average typical dose of cannabis per session in the previous 12 months was higher for STHD ecstasy users compared to STLD ecstasy users and non-ecstasy users. The average dose of cannabis per session in the previous 12 months was higher for STLD ecstasy users relative to non-ecstasy users. Kruskal-Wallis showed that there was a significant difference between the groups in terms of the typical average dose of cannabis use per session in the previous 12 months, $\chi^2(2)=8.29$, $p=.02$. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) showed that STHD ecstasy users consumed higher typical average doses of cannabis use per session in the previous 12 months compared to non-ecstasy users, U=131.00, $p=.008$. The differences between STHD ecstasy users and STLD ecstasy users, U=144.50, $p=.08$, as well as STLD ecstasy users and non-ecstasy users, U=170.50, $p=.13$, were both non-significant. The median data reveals that the average typical dose of cocaine in the previous 12 months was higher for STHD ecstasy users relative to STLD ecstasy users and non-ecstasy users. Mann-Whitney U test showed that the overall group difference was not significant, U=125.50, $p=.42$.

In terms of the average short-term frequency (times per week) of drug use, the median data shows that STHD ecstasy users consumed cannabis more frequently in the previous 12 months compared to STLD ecstasy users and non-ecstasy users. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of average frequency of cannabis use in the previous 12 months, $\chi^2(2)=9.28$, $p=.01$. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) revealed that there was no difference between STHD ecstasy users and STLD ecstasy users in terms of the average frequency of cannabis use in the previous 12 months, U=120.00, $p=.048$. Similarly, there was no difference in the average frequency of cannabis use in the previous 12 months between STHD ecstasy users and STLD ecstasy, U=136.50, $p=.05$, and also STLD ecstasy users and non-ecstasy users, U=184.50, $p=.25$. The median data shows that STHD ecstasy users consumed cocaine more frequently in the previous 12 months compared to STLD ecstasy users. The overall group difference was not significant. Mann-Whitney U test revealed that the groups difference was not statistically significant, U=126.50, $p=.44$.

With regard to recent drug use, the median data shows that STHD ecstasy users had used more cannabis in the 30 days prior to test-session compared to STLD ecstasy users and non-ecstasy users. STLD ecstasy users had used more cannabis in the previous 30 days compared to non-ecstasy users Kruskal-Wallis test showed that there was a significant

difference between the groups in terms of total cannabis consumption in the previous 30 days, $\chi^2(2)=16.73$, $p<.001$. Post hoc Mann-Whitney U tests with full Bonferroni correction (adjusted alpha level=.017) revealed that STHD ecstasy users consumed significantly more cannabis in the previous 30 days than STLD ecstasy users, U=89.50, $p=.004$, and non-ecstasy users U=84.50, $p<.001$. There was no significant difference in the total cannabis consumed in the previous 30 days between STLD ecstasy users and non-ecstasy users, U=184.00, $p=.90$. The median data shows that STHD ecstasy users and STLD ecstasy users had used comparable amounts of cocaine in the 30 days prior to the test-session. The overall group difference was not significant with Mann-Whitney U test showing that the difference was not statistically significant, U=99.00, $p=.32$.

In relation to period of abstinence, the median data indicates that STHD ecstasy users and STLD ecstasy users had used cannabis more recently than non-ecstasy users. The period of abstinence from cannabis use was similar for STHD ecstasy users and STLD ecstasy users. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of the number of weeks since they last used cannabis, $\chi^2(2)=7.05$, $p=.03$. Mann-Whitney U tests showed that STHD ecstasy users had a significantly shorter period of abstinence from cannabis use relative to non-ecstasy users, U=127.00, $p=.01$. The difference between STHD ecstasy users and STLD ecstasy users approached statistical significance, U=135.50, $p=.051$, such that short-term high dose ecstasy users had consumed cannabis more recently than STLD ecstasy users. There was no significant difference between non-ecstasy users and STLD ecstasy users in terms of the number of weeks since they had last used cannabis, U=201.00, $p=.63$.

For descriptive data relating to short-term background drug use variables, see Chapter 7, Table 7.6.

Statistical analyses relating to the short-term dose-related effects of ecstasy use on short-term time-based PM performance whilst controlling for ecstasy use within the previous seven days.

Outcomes for the Karolinska fatigue questionnaire (the percentage of Karolinska fatigue questionnaires completed during the second half of the test-session and the percentage of Karolinska fatigue questionnaires completed overall only) for short-term high-dose ecstasy users, short-term low-dose ecstasy users and non-ecstasy users are summarised in Table 7.9. Those individuals who had used ecstasy in the seven days prior to the test-session were excluded from these analyses.

Table 7.9 Means and Standard Deviations (SD) for short-term high dose ecstasy users, short-term low dose ecstasy users and non-ecstasy users on the Karolinska fatigue PM task (the percentage of Karolinska fatigue questionnaires completed during the second half of the test-session and the percentage of Karolinska fatigue questionnaires completed overall only).

	STHD ecstasy users n=17	STLD ecstasy users n=23	Non-ecstasy users (n=48)	p
	Mean (SD)	Mean (SD)	Mean (SD)	
Karolinska fatigue PM task				
Percentage completed in second half of test-session	39.61 (34.23)	66.81 (23.07)	70.63 (28.97)	.001**
Percentage completed Overall	62.61 (19.13)	77.09 (17.76)	79.38 (19.71)	.01*

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

The data in Table 7.9 shows that that non-ecstasy users successfully completed a higher proportion of Karolinska fatigue questionnaires during the second half of the test-session compared STHD ecstasy users and STLD ecstasy users. STLD ecstasy users also completed a higher proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to STHD ecstasy users. One-way ANOVA revealed a significant difference between the groups in terms of the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session, $F(2, 85)= 7.53$, $p=.001$, partial eta squared=.15. Helmert contrasts showed that compared to non-ecstasy users, the combined group of short-tem high dose ecstasy users and STLD ecstasy users remembered to complete a significantly lower proportion of Karolinska fatigue questionnaires in the second half of the test-session, $p=.01$. Furthermore, relative to STHD ecstasy users, STLD ecstasy users completed a significantly higher proportion of Karolinska fatigue questionnaires in the second half of the test-session, $p=.004$. Pairwise comparisons adjusted by Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users (M=70.68, SD=28.97) completed a significantly greater proportion of Karolinska fatigue questionnaires in the second half of the test-session compared to STHD ecstasy users (M=39.61, SD=34.23), $p<.001$. STLD ecstasy users (M=66.81, SD=23.07) also completed a significantly higher proportion of Karolinska fatigue questionnaires in the second half of the test-session compared to STHD ecstasy users, $p=.004$. There was no significant difference between non-ecstasy users and STLD ecstasy users in terms of the proportion of Karolinska fatigue questionnaires completed in the second half of the test-session, $p=.64$.

Inspection of the data in Table 7.9 reveals that over the entire test-session, non-ecstasy users and STLD ecstasy users completed a higher proportion of Karolinska fatigue questionnaires than STHD ecstasy users. Overall completion rates were comparable between non-ecstasy users and STLD ecstasy users. One-way ANOVA revealed that there was a significant difference between the groups in terms of the overall proportion of Karolinska fatigue questionnaires during the entire test-session, $F(2,85)=4.89$, $p=.01$, partial eta squared=.10. Helmert contrasts showed that non-ecstasy users completed a significantly larger proportion of Karolinska fatigue questionnaires during the entire test-session compared to the combined group of

STHD ecstasy users and STLD ecstasy users, *p*=.02. Short-term lose dose ecstasy users also remembered to complete a significantly larger proportion of Karolinska fatigue questionnaires during the entire test-session compared to STHD ecstasy users, *p*=.02. Pairwise comparisons adjusted for Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users (M=79.38, SD=19.71) completed a significantly larger proportion of Karolinska fatigue questionnaires during the entire test-session compared to STHD ecstasy users (M=62.61, SD=19.13), *p*=.003. The pairwise comparison between STHD ecstasy users and STLD ecstasy users (M=77.09, SD=17.76) approached statistical significance, *p*=.02 such that STHD ecstasy users completed fewer Karolinska fatigue questionnaire during the entire test-session. There was no significant difference in the overall proportion of Karolinska fatigue questionnaires completed during the entire test-session between non-ecstasy users and STLD ecstasy users, *p*=.64.

Appendix 4

Appendix relating to inferential statistics not reported in Chapter 8

Study 1

Demographical data for long-term high alcohol (LTHA) ecstasy users, long-term low alcohol (LTLA) ecstasy users and non-ecstasy users (Study 1).

One-way ANOVA revealed there was a significant age difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $F(2,81)=6.02$, $p=.004$. Tukey's post hoc test showed that non-ecstasy users (M=20.09, SD=2.12) were significantly younger than both LTHA ecstasy users (M=21.80, SD=1.70), $p=.01$ and LTLA ecstasy users (M=21.55, SD=2.39), p=.03. There was no significant difference between LTHA ecstasy users and LTLA ecstasy users in terms of age, $p=.93$.

One-way ANOVA revealed that there was a significant difference between long-term high alcohol ecstasy users, long-term low alcohol ecstasy users and non-ecstasy users in terms of years of education, $F(2,78)=16.62$, $p=.009$. Tukey's post hoc test showed that non-ecstasy users (M=14.55, SD=1.81) had studied for a significantly shorter period of time than long-term high alcohol ecstasy users (M=16.03, SD=1.74), $p=.01$. There was no significant difference between non-ecstasy users and long-term low alcohol ecstasy users (M=15.52, SD=1.93) or long-term high alcohol ecstasy users and long-term low alcohol ecstasy users in terms of number of years of education, $p=.13$, and $p=.67$, respectively.

One-way ANOVA showed that there was a significant difference in the typical number of units of alcohol consumed per week between long-term high alcohol ecstasy users, long-term low alcohol ecstasy users and non-ecstasy users, $F(2,74)=5.96$, $p=.004$. Tukey's post hoc test showed that long-term high alcohol ecstasy users (M=23.59, SD=22.04) consumed significantly more alcohol per week compared to long-term low alcohol ecstasy users (M=10.31, SD=8.63), $p=.02$ and non-ecstasy users (M=9.96, SD=12.11), $p=.004$. There was no significant difference in the typical number of units of alcohol consumed per week by long-term low alcohol ecstasy users and non-ecstasy users, $p=1.00$.

A series of one-way ANOVAs revealed that the groups did not differ significantly in terms of intelligence, F(2,75)=.45, *p*=.64, cigarette consumption, F(2,24)=.20, *p*=.82, Epworth Sleepiness Scale score, F(2,74)=2.64, *p*=.08, arousal, F(2,71)=.16, *p*=.86, anxiety, F(2,70)=2.35, *p*=.10 and depression, F(2,71)=1.30, *p*=.28.

Background drug use data for LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users (Study 1).

LTHA ecstasy users and LTLA ecstasy users did not differ significantly from each other in terms of duration of ecstasy use, U=180.00, *p*=1.00 or the long-term frequency of ecstasy use, U=152.00, *p*=.19.

There was a significant difference in the duration of cannabis use between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $\chi^2(2)=6.24$, p=.04. LTHA ecstasy users had used cannabis for a significantly longer duration of time compared to non-ecstasy users, U=50.00, *p*=.01. However, there was no significant difference in the duration of cannabis use between LTLA ecstasy users and non-ecstasy users, U=52.00, *p*=.06 and LTHA ecstasy users and LTLA ecstasy users, U=125.00, *p*=.06. Total cannabis consumption, the long-term average dose of cannabis per session and the long-term frequency of cannabis use did not differ significantly between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $\chi^2(2)=1.49$, *p*=.48, $\chi^2(2)=1.78$, *p*=.41, , $\chi^2(2)=3.31$, *p*=.19, respectively.

LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users did not differ significantly from each other with regard to total cocaine consumption, U=126.50, *p*=.55, duration of cocaine use, U=91.50, *p*=.31 or long-term frequency of cocaine use, U=117.00, *p*=.39.

Study 2

Demographical data for short-term high alcohol (STHA) ecstasy users, short-term low alcohol (STLA) ecstasy users and non-ecstasy users (Study 2).

One-way ANOVA showed that there was a significant age difference between the STHA ecstasy users, STLA ecstasy users and non-ecstasy, $F(2,83)=5.17$, $p=.008$. Tukey's post hoc test showed that non-ecstasy users (M=20.09, SD=2.12) were significantly younger than STLA ecstasy users (M=23.43, SD=7.17), $p=.005$. There was no significant difference in age between non-ecstasy users and STHA ecstasy users (M=21.33, SD=1.62), $p=.46$ or STHA ecstasy users and STLA ecstasy users, $p=.20$.

One-way ANOVA showed that there was a significant difference between STHA ecstasy users, STLA ecstasy users and non-ecstasy users in terms of the typical number of units of alcohol that they consumed each week, $F(2,78)=3.90$, $p=.02$. Tukey's post-hoc test showed that, on average, STHA ecstasy users (M=21.16, SD=20.93) consumed more units of alcohol per week compared to non-ecstasy users (M=9.96, SD=12.11), $p=.02$. There was no difference in the typical number of units of alcohol consumed each week by non-ecstasy users and STLA ecstasy users (M=12.44, SD=11.44), $p=.82$ or STHA users and STLA ecstasy users, $p=.17$.

A series of one-way ANOVAs revealed that there were no significant differences between the groups in terms of intelligence (Raven's Progressive Matrices), $F(2,76)=.19$, $p=.83$, years of education, $F(2,80)=3.00$, $p=.06$, cigarette consumption, $F(2,25)=.16$, $p=.86$, Epworth Sleepiness Scale Score, $F(2,76)=.25$, $p=.78$, arousal, $F(2,72)=.93$, $p=.40$, anxiety, $F(2,71)=.43$, $p=.65$, and depression, $F(2,72)=.01$, $p=.99$.

Background drug use data for STHA ecstasy users, STLA ecstasy users and non-ecstasy users (Study 1).

A series of Kruskal-Wallis tests showed that STHA ecstasy users, STLA ecstasy users and non-ecstasy users did not differ significant from each other in terms of total cannabis use in the last 12 months, $\chi^2(2)=.79$, $p=.68$, the average typical dose of cannabis per session in the last 12 months, $\chi^2(2)=.63$, $p=.73$, or the number of weeks since cannabis was last used $\chi^2(2)=.95$, $p=.62$.

Appendix 5

Appendix relating to inferential statistics for PM outcomes when concurrent alcohol and ecstasy use is dichotomised according to the product of alcohol and ecstasy use

The paragraphs below correspond to Chapter 8. Inferential statistics are reported for the F1 event-based PM task, the long-term delayed recall PM task, the Karolinska fatigue PM task and the CAMPROMPT when long- and short-term concurrent alcohol and ecstasy use are dichotomised based on the product of alcohol and ecstasy use (rather than based solely on the number of units of alcohol consumed). The product was simply derived by multiplying the mean average dose of ecstasy per session by the number of units of alcohol typically consumed in a session.

Long-term concurrent alcohol and ecstasy use

Method

Participants

Twenty long-term concurrent high-alcohol ecstasy users (LTHA; 14 males), 19 long-term concurrent low-alcohol ecstasy users (LTLA; 12 males) and 44 non-ecstasy users (16 males) took part in the investigation. The gender composition did differ significantly between the groups, $\chi^2(2)=7.27$, $p=.03$. There were more females (n=28) than males (n=16) in the non-ecstasy user group. There were more males (n=12) than females (n=7) in the LTHA ecstasy user group. There were also more males (n=14) than females (n=7) in the LTLA ecstasy user group. Participants were recruited via direct approach to university students.

Materials

As per Chapter 8 (see section 8.2)

Procedure

As per Chapter 8 (see section 8.2)

Design/Statistics

A median split was used to dichotomise long-term concurrent alcohol and ecstasy use. For each year, the typical number of units of alcohol and number of ecstasy tablets consumed in a representative session were recorded. The resulting figures were averaged over the entire period that an individual had used alcohol and ecstasy concurrently (intervening years during which the drug was not used are coded as zero) producing an annual average. The two values (the average number of units of alcohol consumed in a typical session of ecstasy use & the average number of ecstasy tablets consumed in a typical session) were then multiplied together to produce the product of alcohol and ecstasy use and thus create two user groups (LTHA ecstasy users and LTLA ecstasy users). The median value for long-term concurrent alcohol and ecstasy use was 29. Participants who, on average, generated a value greater than 29 per session for the alcohol-ecstasy product (units x tablets) were classified as LTHA ecstasy users and those that consumed less than or equal to 29 product units per session were classified as LTLA ecstasy users. The high and low concurrent alcohol and ecstasy user groups together with a non-ecstasy user group constituted the three levels of the between participant IV.

All PM measures (the F1 event-based Pm task, the long-term delayed recall PM task, the Karolinska fatigue PM task and the CAMPROMPT) were analysed using a between-participant design with user group as the independent variable (LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users).

Results

Outcomes for the F1 event-based PM task, the long-term delayed recall PM task, the Karolinksa fatigue PM task and the CAMPROMPT for LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users are summarised in Table 8.7.

Table 8.7 Mean, Standard Deviations (SD), Median, Minimum (Min.), Maximum (Max.) and Interquartile Range scores for long-term high alcohol ecstasy users, long-term low alcohol ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall Task, the Karolinska fatigue PM task and the CAMPROMPT.

	LTHA ecstasy users n=20					LTLA ecstasy users n=19					Non-ecstasy users n=44					p
	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	
F1 event-based PM task																
Trial 1 Errors	.45 (1.00)	.00	.00	3.00	.00	.61 (1.09)	.00	.00	3.00	1.25	.14 (.65)	.00	.00	3.00	.00	.051
Trial 2 Errors	.15 (.67)	.00	.00	3.00	.00	.33 (.97)	.00	.00	3.00	.00	.00 (.00)	.00	.00	.00	.00	.11
Trial 3 Errors	.10 (.31)	.00	1.00	.00	.00	.28 (.83)	.00	.00	3.00	.00	.05 (.22)	.00	.00	1.00	.00	.58
Total Errors	.70 (1.53)	.00	.00	6.00	.75	1.22 (2.32)	.00	.00	8.00	2.00	.19 (.67)	.00	.00	3.00	.00	.06
Long-term delayed recall PM task																
Total number of recall tests returned (max of 3)	.80 (1.20)	.00	.00	3.00	2.00	.84 (1.17)	.00	.00	3.00	2.00	1.41 (1.42)	1.00	.00	3.00	3.00	.13
Karolinska fatigue PM task																
Percentage completed in first half of test-session	87.79 (14.16)	92.86	60.00	100.00	20.00	82.02 (16.34)	80.00	50.00	100.00	33.33	91.31 (16.00)	100.00	20.00	100.00	20.00	.04*
Percentage completed in second half of test-session	43.50 (38.85)	45.00	.00	100.00	66.25	41.85 (31.74)	33.33	.00	100.00	46.67	79.92 (27.91)	100.00	.00	100.00	27.09	<.001***
Percentage completed overall	64.09 (22.61)	65.15	30.00	100.00	34.10	60.68 (21.40)	58.33	30.00	100.00	33.85	86.09 (17.53)	90.45	27.27	100.00	21.25	<.001***
Cambridge PM test																
Event-based PM performance	15.13 (4.06)	16.00	2.00	18.00	4.00	12.78 (3.57)	13.00	4.00	18.00	4.50	16.95 (1.97)	18.00	8.00	18.00	2.00	<.001***
Time-based PM performance	13.31 (4.39)	15.00	4.00	18.00	5.75	13.33 (3.36)	14.00	4.00	18.00	4.00	17.15 (1.97)	18.00	8.00	18.00	1.50	<.001***
Overall PM performance	28.44 (7.01)	30.00	12.00	36.00	9.75	26.11 (6.45)	28.00	8.00	34.00	6.00	34.15 (3.28)	36.00	20.00	36.00	2.00	<.001***

*p<.05, ***p<.001 *Note*. n for all groups was variable due to missing data. Eighteen long-term low alcohol ecstasy users and 44 non-ecstasy users completed the F1 event-based PM task. Forty-two non-ecstasy users completed the 42 non-ecstasy users completed the Karolinska fatigue PM task. Sixteen long-term high alcohol ecstasy users, 18 long-term low alcohol ecstasy users and 40 non-ecstasy users completed the Cambridge PM test.

The distributions of the data for Trial 1 errors (Skew, z=8.94 and Kurtosis, z=7.73), Trial 2 errors (Skew, z=18.91 and Kurtosis, z=45.39), Trial 3 errors (Skew, z=18.20 and Kurtosis, z=49.10) and total errors (Skew, z=12.09 and Kurtosis, z=21.31) on the F1 event-based PM task, for the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed in the first half of the test-session only, Skew, z=-5.73 and Kurtosis, z=5.87) and for the CAMPROMPT PM test (event-based PM total, Skew, z=-6.76 and Kurtosis, z=6.96, time-based PM total, Skew, z=-5.78, Kurtosis, z=3.91, overall PM, Skew, z=-5.86, Kurtosis, z=4.66) deviated significantly from normality. This was characterised by the skew and/or kurtosis z scores exceeding 3.29, $p<.001$ (Tabachnick & Fidell, 2001). Group differences were investigated via Kruskal-Wallis test with follow-up post hoc Mann-Whitney U tests (with full Bonferroni correction, adjusted alpha level=.017).

Where the distributions were normal, one-way ANOVAs were used to investigate group differences on two aspects of the Karolinska fatigue PM task (proportion of Karolinska fatigue questionnaires completed in the second half of the test-session and overall proportion of Karolinska fatigue questionnaires completed during the first and second half of the test-session) and the long-term delayed recall PM task. ANOVAs were followed up with Helmert contrasts and pairwise comparisons.

Examination of the data in Table 8.7 reveals that LTHA ecstasy users and LTLA ecstasy users made more errors than non-ecstasy users on all trials of the F1 event-based PM task. LTLA ecstasy users made more errors than LTHA users on all trials of the F1 event-based PM task. There was no significant difference in the number of errors that were made on trial 1 of the F1 event-based PM task by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $\chi^2(2)=5.97$, $p=.051$, although this effect did approach statistical significance. LTLA ecstasy users made significantly more errors on the trial 1 of the F1 event-based PM task compared to non-ecstasy users, U=294.00, $p=.015$. There was no significant difference in the number of errors that were made on trial 1 of the F1 event based PM task between LTHA ecstasy users and non-ecstasy users, U=358.00, $p=.07$ or LTHA ecstasy users and LTLA ecstasy users, U=166.50, $p=.60$.

There was no significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of the numbers of errors that were made on trial 2 $\chi^2(2)=4.37$, p=.11 and trial 3, $\chi^2(2)=1.08$, p=.58 of the F1 event-based PM task. In addition, no significant difference was found in total errors made on the F1 event-based PM task by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $\chi^2(2)=5.72$, p=.06. Nonetheless, this effect did approach statistical significance. Post hoc tests showed that there was no significant difference between LTHA ecstasy users and non-ecstasy users, U=353.00, *p*=.10 or LTHA ecstasy users and LTLA ecstasy users, U=162.00, *p*=.61 in terms of the overall errors made on F1 event-based PM task. The difference between LTLA ecstasy users and non-ecstasy users, approached statistical significance such that LTLA made more errors than non-ecstasy users, U=284.00, *p*=.019.

With regard to long-term time-based PM performance, the data in Table 8.7 reveals that non-ecstasy users returned more delayed recall test sheets (long-term delayed recall PM task) than both LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users also returned more delayed recall test sheets compared to LTLA ecstasy users. One-way ANOVA revealed that there was no significant difference in the number of delayed recall test sheets returned by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, F(2,80)=2.08, *p*=.13, partial eta squared=.05.

Table 8.7 shows that compared to LTHA ecstasy users and LTLA ecstasy users, non-ecstasy users successfully completed a greater number of Karolinska fatigue questionnaires during the first and second half of the test-session. Overall performance on the Karolinska fatigue questionnaire was better for non-ecstasy users compared to LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users and LTLA ecstasy users completed a similar proportion of Karolinska fatigue questionnaires during the first and second half of the test-session. In addition, overall performance on the Karolinska fatigue PM task was comparable between LTHA ecstasy users and LTLA ecstasy users.

There was a significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of the proportion of Karolinska fatigue questionnaires that were completed during the first half of the test-session, $\chi^2(2)=6.27$, *p*=.04. Non-ecstasy users completed a significantly larger proportion of Karolinska

fatigue questionnaires than LTLA ecstasy users during the first half of the test-session, U=259.50, *p*=.014. There was no significant difference in the proportion of Karolinksa fatigue questionnaires completed during the first half of the test-session between LTHA ecstasy users and non-ecstasy users, U=350.50, *p*=.23 or LTHA ecstasy users and LTLA ecstasy users, U=148.50, *p*=.22.

One-way ANOVA revealed that there was a significant difference in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session by LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users, $F(2,78)=14.96$, $p<.001$, partial eta squared=.28. Helmert contrast showed that compared to non-ecstasy users, the combined group of LTHA ecstasy users and LTLA ecstasy users completed a significantly lower proportion of Karolinska fatigue questionnaires during the second half of the test-session, $p<.001$. A further Helmert contrast revealed that there was no significant difference in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session by LTHA ecstasy users and LTLA ecstasy users, $p=.87$. Pairwise comparisons adjusted for full Bonferroni correction (significant alpha level=.017) revealed that non-ecstasy users competed a significantly greater proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to LTHA ecstasy users, $p<.001$ and LTLA ecstasy users, $p<.001$. There was no significant difference in the proportion of Karolinska fatigue questionnaires completed during the second half of the test-session by LTHA ecstasy users and LTLA ecstasy users, $p=.87$.

One-way ANOVA showed that there was a significant difference between LTHA ecstasy users, LTLA ecstasy users and non-ecstasy users in terms of the overall completion rate of Karolinska fatigue questionnaire, $F(2,78)=14.59$, $p<.001$, partial eta squared=.28. Helmert contrast showed that non-ecstasy users completed a significantly greater proportion of Karolinska fatigue questionnaires overall compared to the combined group of LTHA ecstasy users and LTLA ecstasy users, $p<.001$. A further Helmert contrast showed that there was no significant difference between LTHA ecstasy users and LTLA ecstasy users in terms of the proportion of Karolinka fatigue questionnaires completed overall, $p=.59$. Pairwise comparisons adjusted for full Bonferroni correction (significant alpha level=.017) revealed that non-ecstasy users competed a significantly higher proportion of Karolinska fatigue questionnaires overall compared to LTHA ecstasy users, $p<001$ and LTLA ecstasy users, $p<.001$.

There was no significant difference in the proportion of Karolinska fatigue questionnaires completed overall by LTHA ecstasy users and LTLA ecstasy users, p=.59.

Table 8.7 shows that non-ecstasy users successfully completed more event-based PM tasks on the CAMPROMPT compared to LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users also completed more time-based PM tasks on the CAMPROMPT than LTLA ecstasy users. The overall group difference was significant, $\chi^2(2)=24.84$, $p<.001$. Non-ecstasy users were significantly better at completing event-based PM tasks on the CAMPROMPT than LTLA ecstasy users, U=86.50, $p<.001$. No significant difference was found between non-ecstasy users and LTHA ecstasy users, U=212.50, p=.03 or LTHA ecstasy users and LTLA ecstasy users, U=80.00, p=.017. Both group differences approached statistical significance.

The data in Table 8.7 indicate that non-ecstasy users successfully completed more time-based PM tasks on the CAMPROMPT compared to LTHA ecstasy users and LTLA ecstasy users. LTHA ecstasy users and LTLA ecstasy users completed a similar number of time-based PM tasks on the CAMPROMPT. A significant difference was found between the groups in terms of time-based PM performance on the CAMPROMPT, $\chi^2(2)=31.52$, $p<.001$. Non-ecstasy users completed significantly more time-based PM tasks on the CAMPROMPT than LTHA ecstasy users, U=116.50, $p<.001$, and LTLA users, U=78.50, $p<.001$. No significant difference was found between LTHA ecstasy users and LTLA ecstasy users in terms of time based PM performance on the CAMPROMPT, U=132.00, p=.67

In terms of overall PM performance on the CAMPROMPT, the data in Table 8.7 indicate that non-ecstasy users performed better than LTHA ecstasy users and LTLA ecstasy users. In addition, overall performance on the CAMPROMPT was slightly worse for LTLA ecstasy users compared to LTHA ecstasy users. There was a significant group difference in overall PM performance on the CAMPROMPT, χ^2 (2)=32.99, $p<.001$. Overall PM performance on the CAMPROMPT was significantly higher for non-ecstasy users compared to LTHA ecstasy users, U=129.50 $p<.001$, and LTLA ecstasy users, U=48.00, $p<.001$. There was no significant difference in overall PM performance on the CAMPROMPT between LTHA ecstasy users and LTLA ecstasy, U=106.50, p=.19.

Short-term concurrent alcohol and ecstasy use

Method

Participants

Twenty-one short-term concurrent high alcohol ecstasy users (STHA; 14 males), 21 short-term concurrent low alcohol ecstasy users (STLA; 14 males) and 44 non-ecstasy users (16 males) took part in the investigation. The gender composition did differ significantly between the groups, $\chi 2(2)=7.90$, $p=.02$. There were more females (n=28) than males (n=16) in the non-ecstasy user group. There were more males (n=14) than females (n=7) in the STHA ecstasy user group. There were also more males (n=14) than females (n=7) in the STLA ecstasy user group. Participants were recruited via direct approach to university students.

Materials

As per Chapter 8 (see section 8.4)

Procedure

As per Chapter 8 (see section 8.4)

Design/Statistics

A median split was used to dichotomise short-term concurrent alcohol and ecstasy use. For each month in the 12-months prior to the test-session, the typical number of units of alcohol and number of ecstasy tablets consumed in a representative session were recorded. The resulting figures were averaged over the 12-month period (intervening months during which the drug was not used are coded as zero) producing an annual average. The two values (the average number of units of alcohol consumed in a typical session of ecstasy use & the average number of ecstasy tablets consumed in a typical session) were then multiplied together to produce a product of alcohol and ecstasy use and thus create two user groups (STHA ecstasy users and STLA ecstasy users). The median value for short-term concurrent alcohol and ecstasy use was .53 (the product unit value is very low reflecting the fact that many users were effectively abstinent during the 12 months prior to the test-session.) Participants who, on average,

consumed a combined value of .53 units of alcohol and ecstasy tablets per session (units x tablets) were classified as STHA ecstasy users and those that consumed less than .53 product units were classified as STLA ecstasy users. The high and low concurrent alcohol and ecstasy user groups together with a non-ecstasy user group constituted the three levels of the between participant IV.

All PM measures (the F1 event-based Pm task, the long-term delayed recall PM task, the Karolinska fatigue PM task and the CAMPROMPT) were analysed using a between-participant design with user group as the independent variable (STHA ecstasy users, STLA ecstasy users and non-ecstasy users).

Results

Outcomes for the laboratory-based measures of PM (the F1 event-based PM task, the long-term delayed recall PM task, the Karolinksa fatigue PM task and the CAMPROMPT) for STHA ecstasy users, STLA ecstasy users and non-ecstasy users are summarised in Table 8.8.

Table 8.8 Mean, Standard Deviations (SD), Median, Minimum (Min.), Maximum (Max.) and Interquartile Range scores for short-term high alcohol ecstasy users, short-term low alcohol ecstasy users and non-ecstasy users on the F1 event-based PM task, the long-term delayed recall Task, the Karolinska fatigue PM task and the CAMPROMPT.

	STHA ecstasy users n=21					STLA ecstasy users n=20					Non-ecstasy users n=44					p
	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	Mean (SD)	Median	Min.	Max.	Int. Range	
F1 event-based PM task																
Trial 1 Errors	.55 (1.05)	.00	.00	3.00	.75	.60 (1.14)	.00	.00	3.00	.75	.14 (.65)	.00	.00	3.00	.00	.045*
Trial 2 Errors	.15 (.67)	.00	.00	3.00	.00	.30 (.92)	.00	.00	3.00	.00	.00 (.00)	.00	.00	.00	.00	.14
Trial 3 Errors	.00 (.00)	.00	.00	.00	.00	.35 (.81)	.00	.00	3.00	.00	.05 (.22)	.00	.00	1.00	.00	.03*
Total Errors	.70 (1.53)	.00	.00	6.00	.75	1.25 (2.24)	.00	.00	8.00	2.00	.19 (.67)	.00	3.00	.00	.00	.04*
Long-term delayed recall PM task																
Total number of recall tests returned (max of 3)	.71 (1.15)	.00	.00	3.00	1.50	.85 (1.18)	.00	.00	3.00	2.00	1.41 (1.42)	1.00	.00	3.00	3.00	.09
Karolinska fatigue PM task																
Percentage completed in first half of test-session	84.24 (17.48)	85.71	50.00	100.00	33.34	86.42 (12.57)	81.67	60.00	100.00	20.00	91.31 (16.00)	100.00	20.00	100.00	20.00	.10
Percentage completed in second half of test-session	38.82 (31.89)	33.33	.00	100.00	58.34	47.51 (32.53)	40.00	.00	100.00	49.11	79.92 (27.91)	100.00	.00	100.00	27.09	<.001***
Percentage completed overall	59.83 (20.54)	58.33	30.00	100.00	28.87	64.75 (22.43)	60.00	30.00	100.00	32.89	86.09 (17.53)	90.54	27.27	100.00	21.25	<.001***
Cambridge PM test																
Event-based PM performance	14.20 (3.94)	15.00	2.00	18.00	5.50	13.38 (3.91)	15.00	4.00	18.00	5.50	16.95 (1.97)	18.00	8.00	18.00	2.00	<.001***
Time-based PM performance	14.35 (3.69)	16.00	4.00	18.00	3.50	12.25 (3.71)	13.00	4.00	18.00	3.50	17.15 (1.97)	18.00	8.00	18.00	1.50	<.001***
Overall PM performance	28.55 (6.77)	30.00	12.00	36.00	7.50	25.62 (6.42)	26.00	8.00	36.00	6.00	34.10 (3.28)	36.00	20.00	36.00	2.00	<.001***

*p<.05, ***p<.001 *Note*. n for all groups was variable due to missing data. Twenty short-term high alcohol ecstasy users completed the F1 event-based PM task. Twenty short-term high alcohol ecstasy users, 16 short-term low alcohol ecstasy users and 40 non-ecstasy users completed the Cambridge PM test.

Table 8.8 shows that STHA ecstasy users and STLA ecstasy users made more errors than non-ecstasy users on trial 1 of the F1 event-based PM task while the two concurrent alcohol and ecstasy user groups performed similarly. The overall group difference was significant, $\chi^2(2)=6.21$, $p=.045$. However, no significant differences were found between STHA ecstasy users and non-ecstasy users, U=338.00, $p=.03$, STLA ecstasy users and non-ecstasy users, U=337.00, $p=.02$ or STHA ecstasy users and STLA ecstasy users, U=198.00, $p=.97$. Nonetheless, in the first two cases the pairwise comparisons approached significance with non-ecstasy users making fewer errors.

The data in Table 8.8 indicate that STHA ecstasy users and STLA ecstasy users made more errors than non-ecstasy users on trial 2 of the F1 event-based PM task. STLA ecstasy users also made more errors than STHA ecstasy users on trial 2 of the F1 event-based PM task. The overall group difference was not significant, $\chi^2(2)=3.93$, $p=.14$

Inspection of Table 8.8reveals that STLA ecstasy users made more errors than both STHA ecstasy users and non-ecstasy users on trial 3 of the F1 event-based PM task while STHA ecstasy users and non-ecstasy users performed comparably. Contrary to expectation, STHA ecstasy users appear to have made no errors at all on trial 3 of the F1 event-based PM task. The overall group difference was significant, $\chi^2(2)=6.86$, $p=.03$. However, none of the pairwise comparisons were significant: for STHA ecstasy users versus non-ecstasy users, U=400.00, $p=.33$, STLA ecstasy users versus non-ecstasy users, U=354.00, $p=.05$, and for STHA ecstasy users versus STLA ecstasy users, U=160.00, $p=.29$.

In terms of overall performance on the F1 event-based PM task, the data in Table 8.8 show that STHA ecstasy users and STLA ecstasy users made more errors than non-ecstasy users. STLA ecstasy users made more errors overall than STHA ecstasy users. The group difference in the number of errors made across all trails of the F1 event-based PM task was significant, $\chi^2(2)=6.65$, p=.04. STLA ecstasy users committed significantly more errors overall relative to non-ecstasy users, U=30.00, $p=.011$. There was no significant difference between STHA ecstasy users and non-ecstasy users in the total errors committed on the F1 event based PM task, U=353.00, $p=.10$ nor between STHA ecstasy users and STLA ecstasy users, U=176.50, $p=.53$.

In relation to long-term time-based PM performance, Table 8.8 shows that STHA ecstasy users returned a smaller number of delayed recall tests (the long-term delayed recall test) compared to STLA ecstasy users and non-ecstasy users. STLA ecstasy users remembered to return slightly fewer delayed recall tests than non-ecstasy users. One-way ANOVA showed that the group difference in the number of delayed recall test sheets returned approached statistical significance, $F(2, 82)=2.52$, $p=.09$, partial eta squared=.06. Helmert contrast revealed that the combined group of STHA ecstasy users and STLA ecstasy users returned significantly fewer delayed recall tests that non-ecstasy users, $p=.03$. A further Helmert contrast showed that there was no significant difference between STHA ecstasy users and STLA ecstasy users in terms of the number of delayed recall test that were returned, $p=.74$. Pairwise comparisons with Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that there was no significant difference between STHA ecstasy users and non-ecstasy users, $p=.05$, STLA ecstasy users and non-ecstasy users, $p=.12$, or STHA ecstasy users and STLA ecstasy users, $p=.41$ in terms of the number of delayed recall tests that were returned on the long-term delayed recall task.

Table 8.8 shows that compared to STHA ecstasy users and STLA ecstasy users, non-ecstasy users successfully completed a greater number of Karolinska fatigue questionnaires during the first and second halves of the test-session. Overall performance on the Karolinska fatigue questionnaire was better for non-ecstasy users compared to STHA ecstasy users and non-ecstasy users. STHA ecstasy users and LTLA ecstasy users completed a similar proportion of Karolinska fatigue questionnaires during the first half of the test-session. However, compared to STHA ecstasy users, STLA ecstasy users remembered to complete more Karolinska fatigue questionnaires during the second half of the test-session. Overall performance on the Karolinska fatigue PM task was comparable between STHA ecstasy users and STLA ecstasy users.

There was no significant difference between the groups in terms of the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session, $\chi^2(2)=4.62$, $p=.10$. Post-hoc tests showed that that there was no significant difference in the proportion of Karolinska fatigue questionnaires completed during the first half of the test-session by STHA ecstasy users and non-

ecstasy users, U=334.00, p=.07, STLA ecstasy users and non-ecstasy users, U=316.00, p=.08 or STHA ecstasy users and STLA ecstasy users, U=203.00, p=.85.

One-way ANOVA showed that there was a significant difference between the groups in terms of the proportion of Karolinska fatigue questionnaires that were completed during the second half of the test-session, F(2,80)=17.10, p<.001, partial eta squared=.30. Helmert contrast showed that relative to non-ecstasy users, the combined group of STHA ecstasy users and STLA ecstasy users remembered to completed a significantly higher proportion of Karolinska fatigue questionnaires during the second half of the test-session, p<.001. However, a further Helmert contrast showed that there was no significant difference between STHA ecstasy users and STLA ecstasy users in terms of the proportion of Karolinska fatigue questionnaires that were completed during the second half of the test-session, p=.26. Pairwise comparisons with Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users remembered to complete a significantly higher proportion of Karolinska fatigue questionnaires during the second half of the test-session compared to both STHA ecstasy users, p<.001 and STLA ecstasy users, p<.001. There was no significant difference in the proportion of Karolinska fatigue questionnaires that were completed during the second half of the test-session between STHA ecstasy users and STLA ecstasy users, p=.26.

One-way ANOVA revealed that there was a significant difference between STHA ecstasy users, STLA ecstasy users and non-ecstasy users in terms of overall performance on the Karolinska fatigue PM task, F(2,80)=15.76, p<.001, partial eta squared=.28. Helmert contrast showed that relative to non-ecstasy users, the combined group of STHA ecstasy users and STLA ecstasy users remembered to complete a significantly smaller proportion of Karolinska fatigue questionnaires during the entire test-session, p<.001. However, a further Helmert contrast showed that there was no significant difference between STHA ecstasy users and STLA ecstasy users in terms of the proportion of Karolinska fatigue questionnaires that were completed over during the entire test-session, p=.42. Pairwise comparisons with Bonferroni correction (three pairwise comparisons, significant alpha level set at .017) revealed that non-ecstasy users remembered to complete a significantly higher proportion of Karolinska fatigue questionnaires during the entire test-session compared to both STHA ecstasy users, p<.001 and STLA ecstasy users, p<.001.

There was no significant difference in the proportion of Karolinska fatigue questionnaires that were completed during the entire test-session by STHA ecstasy users and STLA ecstasy users, p=.42.

Examination of the data in Table 8.8 show that non-ecstasy users successfully completed more event-based PM tasks on the CAMPROMPT compared to STHA ecstasy users and STLA ecstasy users. STHA ecstasy completed a similar number of event-based PM tasks on the CAMPROMPT compared to STLA ecstasy users. Kruskal-Wallis test showed that there was a significant group difference in terms of event-based PM performance on the CAMPROMPT, $\chi^2(2)=21.09$, $p<.001$. Non-ecstasy users were significantly better at completing event-based PM tasks on the CAMPROMPT than STHA ecstasy users, U=194.00, $p<.001$ and STLA ecstasy users, U=114.50.00, $p<.001$. No significant difference was found between STHA ecstasy users and STLA ecstasy users in terms of event based PM performance on the CAMPROMPT, U=136.50, p=.44.

Inspection of the data in Table 8.8 reveal that non-ecstasy users successfully completed more time-based PM tasks on the CAMPROMPT compared to STHA ecstasy users and STLA ecstasy users. STHA ecstasy users and STLA ecstasy users completed a similar number of time-based PM tasks on the CAMPROMPT. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of time-based PM performance on the CAMPROMPT, $\chi^2(2)=32.97$, $p<.001$. Non-ecstasy users completed a significantly higher number of time-based PM tasks on the CAMPROMPT than STHA ecstasy users, U=163.50, $p<.001$, and STLA ecstasy users, U=58.00, $p<.001$. No significant difference was found between STHA ecstasy users and STLA ecstasy users in terms of time based PM performance on the CAMPROMPT, U=98.00, p=.04.

In terms of overall PM performance on the CAMPROMPT, Table 8.8 indicates that non-ecstasy users performed better than STHA ecstasy users and STLA ecstasy users. In addition, overall performance on the CAMPROMPT was comparable between STLA ecstasy users compared to STHA ecstasy users. Kruskal-Wallis test showed that there was a significant difference between the groups in terms of overall PM performance on the CAMPROMPT, $\chi^2(2)=33.36$, $p<.001$. Overall PM performance on the CAMPROMPT was significantly higher for non-ecstasy users compared to

STHA ecstasy users, U=135.00, $p<.001$, and STLA ecstasy users, U=56.50, $p<.001$. There was no significant difference in overall PM performance on the CAMPROMPT between STHA ectasy users and STLA ecstasy, U=103.50, $p=.07$.

Appendix 6

Appendix relating to demographic and background drug use data not reported in Chapter 10

Demographical data for ecstasy users and non-ecstasy users.

Independent t-tests revealed that ecstasy users were significantly older, t(84)=2.68, p=.009, had studied for a significantly longer period of time, t(81)=2.24, *p*=.03 and typically consumed significantly more units of alcohol per week, t(77)=2.08, *p*=.04, compared to non-ecstasy users. A number of other independent t-tests were performed which showed that there was no significant difference between ecstasy users and non-ecstasy users in terms of intelligence, t(77)=.41, *p*=.68, cigarette consumption, t(26)=-.42, *p*=.68, Epworth Sleepiness Scale score, t(77)=.70, *p*=.48, arousal, t(73)=-.23, *p*=.82, anxiety, t(72)=.77, *p*=.44 and depression, t(73)=-.06, *p*=.95.

Background drug use data relating to cannabis use for ecstasy users and non-ecstasy users.

A series of Mann-Whitney U tests showed that there was no significant difference between ecstasy users and non-ecstasy users in terms of total lifetime cannabis consumption, U=113.00, *p*=.48, number of cannabis joints smoked in the previous 30 days, U=134.50, *p*=.96, current frequency of cannabis use, U=197.50, *p*=.87 and the number of weeks since cannabis was last used, U=208.00, *p*=.96.

Appendix 7

Appendix relating to published research papers resulting from the data collected during the current Ph.D project.

Title

Prospective memory deficits in illicit polydrug users are associated with the average long term typical dose of ecstasy typically consumed in a single session.

Abstract

Rationale Neuroimaging evidence suggests that ecstasy-related reductions in SERT densities relate more closely to the number of tablets typically consumed per session rather than estimated total lifetime use. In order to better understand the basis of drug related deficits in prospective memory (PM) we explored the association between PM and average long-term typical dose and long-term frequency of use. **Method** *Study 1*: Sixty five ecstasy/polydrug users and 85 non-ecstasy users completed an event based, a short-term and a long-term time based PM task. *Study 2*: Study 1 data were merged with outcomes on the same PM measures from a previous study creating a combined sample of 103 ecstasy/polydrug users, 38 cannabis-only users and 65 nonusers of illicit drugs. **Results** *Study 1*: Ecstasy/polydrug users had significant impairments on all PM outcomes compared to non-ecstasy users. *Study 2*: Ecstasy/polydrug users were impaired in event based PM compared to both other groups and in long-term time based PM compared to non illicit drug users. Both drug using groups did worse on the short-term time based PM task compared to nonusers. Higher long-term average typical dose of ecstasy was associated with poorer performance on the event and short-term time based PM tasks and accounted for unique variance in the two PM measures over and above the variance associated with cannabis and cocaine use. **Conclusions** The typical ecstasy dose consumed in a single session is an important predictor of PM impairments with higher doses reflecting increasing tolerance giving rise to greater PM impairment.

Key words: ecstasy, cannabis, cocaine, prospective memory, dose, tolerance.

INTRODUCTION

The aim of the present paper is to identify which aspects of long term ecstasy/polydrug use are associated with drug-related impairments of prospective memory (PM). PM is an aspect of real-world memory that involves remembering to carry out intended actions in the future (Einstein et al. 2005). PM tasks include both short-term and long-term activities that are triggered by external events (event-based) or the passage of time (time-based). In short-term PM tasks, such as locking the car after leaving, there is a relatively short period of time between the external episode/prompt (leaving the car) and the appropriate behaviour (locking the doors). Long-term PM tasks, such as remembering to post a birthday card, have a longer time interval between the external episode/prompt (realization of a friend's birthday) and the desired behaviour (posting a card). As to the cerebral mechanisms involved in PM processing, there is a general consensus that medial temporal hippocampal structures feature prominently (Adda, Castro, Além-Mar e Silva, de Manreza, & Kashiara, 2008; Martins et al., 2007) as well as areas of the prefrontal cortex (PFC; Brooks, Rose, Potter, Jayawardena, & Morling, 2004; Burgess, Scott, & Frith, 2003; Katai, Maruyuma, Hashimoto, & Ikeda, 2003). Considering that ecstasy users (Kish et al. 2010) and cannabis users (Jager et al. 2007) exhibit abnormalities in these brain regions, it is plausible to suggest that people using these drugs may demonstrate PM impairment. This proposal has received support with several studies using both self report and laboratory based measures demonstrating PM deficits in temporarily abstinent illicit substance users (e.g., Hadjiefthyvoulou, Fisk, Montgomery, & Bridges, 2011a; Heffernan, Jarvis, Rodgers, Scholey, & Ling, 2001a; Montgomery & Fisk, 2007; Rendell, Gray, Henry, & Tolan, 2007). Furthermore, former users of ecstasy have also exhibited event and time-based impairments in PM on the "Virtual Week" task (Rendell, Mazur, & Henry, 2009) highlighting the possible long-term neurotoxic potential of MDMA use.

One key aspect that remains to be thoroughly explored is the presence of dose-related effects in relation to PM performance. It is important to demonstrate that these exist since in the absence of clear dose-related effects, any group differences that have been observed might more readily be attributed to some premorbid condition or lifestyle differences unrelated to drug use. However, in relation to ecstasy use and PM outcomes, there have been some problems with the way in which dose-related effects have been investigated. For example, in between group comparisons, using the self-report Prospective Memory Questionnaire (PMQ), while ecstasy/polydug related PM deficits have emerged in a number of studies, dose related effects have not been directly reported (Heffernan et al. 2001a; Heffernan, Ling, & Scholey, 2001b; Parrott et al. 2006). In other studies, lifetime use has been defined in a categorical manner in terms of the number of times that the drug has been previously used (e.g., 0, 1-9, 10-99, 100+ times). On this basis, lifetime use accounted for unique variance in long term PM problems on the PMQ, but not short term and internally cued PM problems (Rodgers et al. 2001). Montgomery and Fisk (2007) estimated lifetime use in terms of the number of tablets previously consumed but found no association between this variable and outcomes on the PMQ. Bedi and Redman (2008a) obtained estimates of lifetime ecstasy use (total number of tablets) from their participants as well as age of first use, and period of abstinence but none of these significantly predicted PMQ outcomes.

Using objective measures of PM, Zakzanis, Young and Campbell (2003) found that ecstasy users differed from nonusers on the ‘appointment’ and ‘message’ PM subscales of the Rivermead Behavioural Memory Test (RBMT). Furthermore, the scores on the appointment subscale were significantly related to the number of occasions of ecstasy use and to the frequency of use (although the significant outcome was based on a sample size of fewer than 20). Bedi and Redman (2008b) included short term time and event based PM tasks in their test battery but ecstasy/polydrug group differences were either absent or inconclusive and

dose related effects were not reported. Although Rendell et al. (2007) did not report effects in relation to lifetime dose, they found that frequent ecstasy users (using more than once a fortnight) performed worse than infrequent users (using less than one a month) who in turn performed worse than nonusers on all PM measures on the virtual week task. Hadjiefthyvoulou and co-workers found that lifetime ecstasy use (estimated number of tablets) was significantly associated with time and event based PM scores on the Cambridge Prospective Memory Test (CAMPROMPT) (Hadjiefthyvoulou et al. 2011a) and with performance on the RBMT and other short term time and event based PM tasks (Hadjiefthyvoulou et al. 2011b). However, these effects were no longer significant following controls for other drug use. It is also worthy of note that in these studies (Hadjiefthyvoulou et al. 2011a; 2011b; Montgomery & Fisk, 2007) non users were included in the samples (with use coded as zero). Indeed this practice is common in much of the ecstasy-related behavioural research (e.g., Medina, Shear & Corcoran, 2005; Montgomery, Fisk, Newcombe, & Murphy, 2005; Piechatzek et al. 2009; Reneman et al. 2001).

What this summary of the relevant literature demonstrates is that the issue of dose related effects in relation to laboratory measures of PM remains to be systematically investigated. For example, those studies quantifying use in a categorical manner may lose a degree of precision due to the ordinal nature of the scale and responses at the top end of the scale, e.g., 100+, do not reflect the actual differences among heavy users. Furthermore, when lifetime use is defined in terms of occasions of use, differences between individuals who might consume one tablet per occasion, versus others who might consume several tablets are masked. When dose-related effects are reported on the basis of distinctions between broadly defined groups, for example ‘heavy’ versus ‘moderate users’ or ‘frequent’ versus ‘infrequent users’ (e.g., Rendell et al. 2007), the group criteria are variable and even where the same criteria are used widely different cut off points may be adopted. Clearly, comparisons

between user groups defined in this manner might be useful but they are less informative than correlational indicators and make informed comparisons between studies difficult, if not impossible. Including non users of specific drugs in the sample (with their use coded as zero) when dose-related effects are evaluated is also potentially problematic since a significant correlation or regression coefficient may be due to the absence of use within the drug naïve participants (i.e., the group effect) rather than a trend **within** the drug using participants. Indeed when the correlation is limited to the drug users within the sample it may no longer be significant.

Lastly, it is also possible that that estimates of lifetime use which do not suffer from the limitations identified above may still fail to capture subtle differences in the patterns of use between ecstasy users. Consistent with this possibility, Morefield, Keane, Felgate, White, and Irvine (2011) found that there were pronounced differences in the consumption patterns of their sample in terms of the number of tablets consumed in a single session. Furthermore they found that a non linear relationship existed between the number of tablets consumed in a single session and MDMA plasma concentrations with the latter increasing exponentially with the number of tablets consumed. Thus for those consuming no more than a single tablet, MDMA plasma concentrations peaked and remained stable after an hour or so, while those consuming more than a single tablet experienced a dose related disproportionate rise in plasma levels which continued to increase through out the five hour period during which levels were monitored. Therefore, taking a single tablet often or multiple tablets infrequently may give rise to similar lifetime doses but have very different consequences in terms of the typical level and peak duration of blood plasma MDMA levels.

A potential implication of this is that more emphasis should be placed on the size of the typical dose rather than other measures such as frequency of use and lifetime dose. The importance of alternative measures has also emerged from neuroimaging studies. For

example, Thomasius et al. (2003) found that distribution volume ratios (DVRs) of SERT ligands in some sub-cortical structures were best predicted by the usual dose of ecstasy consumed at a typical party event, while in other instances DVRs were best predicted by the amount of ecstasy consumed in the 12 months prior to testing. Estimates of lifetime use and maximum dose of ecstasy were either non significant or accounted for significantly less unique variance.

The present study aimed to further investigate dose related effects on PM performance by using a timeline technique similar to that adopted by Medina et al. (2005) and Bedi and Redman (2008b) in order to examine long term dose related effects . For each illicit drug, we will obtain an estimate of the typical dose and frequency of use for each year since use commenced. These two variables have received relatively little attention previously. Furthermore they can be used to produce an estimate of lifetime use. In the analysis of dose related relationships presented here only users of specific drugs will be included. Non users will be excluded from these particular analyses and we will seek to maximise the size of the available sample by combining samples from different phases of data collection. In Study 1, a replication and extension of previous findings are presented. In Study 2, data from Study 1 will be augmented with equivalent data which, although collected in a previous study, has yet to be analysed. The resulting combined data set will allow us to more effectively investigate polydrug dose related effects. Specifically Study 2 will focus on the effects of the long term average number of tablets consumed in a single session and the long term average frequency of use.

STUDY 1

METHOD

Participants.

Participants included 65 ecstasy/polydrug users (27 females, 37 males, 1 not reported), and 85 non-ecstasy users (54 females) (for demographic details see Table 1). Females predominated among the non-ecstasy user group and males among the ecstasy/polydrug users, producing a significant gender effect, $\chi 2$ (1) =6.70, $p<.01$. Participants, who were university students studying in the United Kingdom, were recruited via direct approach. Fifty-seven of the participants included here took part in a previous study from our laboratory. However, their results on the laboratory PM tasks have not been previously reported and are presented here for the first time. None of the present sample reported use of ecstasy within the week prior to testing and none reported using any other illicit drug within the 24 hours prior to testing. All participants gave verbal consent and were tested in accordance with the national and local ethics guidelines and the Declaration of Helsinki.

Materials

The use of ecstasy and other drugs was assessed by means of a self-report questionnaire previously used in several studies from our laboratory. For all illicit drugs that were regularly consumed and for each year since they commenced drug use, participants estimated the typical dose that they ingested in a representative session and their typical frequency of use (number of sessions per week) during that year. These annual estimates were used to produce an estimate of total lifetime use. Participants also indicated their current frequency of use and the period of abstinence for each major illicit drug. Demographic variables including age, gender, and years of full time education were recorded and fluid

intelligence was measured through Raven's progressive matrices (Raven, Raven & Court, 1998). The current use of cigarettes and alcohol were also recorded.

Laboratory Measures of Prospective Memory.

Pattern Recognition PM Task: This test utilises a processing speed task which was amended to include a parallel PM element. The task involved classifying pairs of patterns which increased in complexity as either the same or different while remembering to press the F1 key each time that the complexity level increased (purportedly to save the participant's scores). The task was repeated three times. The number of times the participant forgot to press F1 for each trial was calculated producing a laboratory event-based PM measure.

Fatigue Short-Term Time-Based PM Test: Following the briefing, participants were told that they should provide an indication of their level of fatigue (using the Karolinska Sleepiness Scale: Gillberg, Kecklund, & Akerstedt, 1994) every 20 minutes throughout the experiment or if this occurred during the completion of a task, to do so immediately after. The percentage of occasions on which this was done was calculated separately for the first and second half of the test session thereby producing two measures of short-term time-based PM. On each occasion, participants who forgot were reminded to fill in the questionnaire.

Mail Long-Term Time Based PM Test: During the test session participants learned a list of 15 words over five trails. A long-term PM element was added in which participants had to remember to return an answer sheet, in a prepaid envelope, to the experimenter with the words that they were able to recall after a delay of one, two, and three weeks from the time of testing. Participants scored 1 if the envelope was returned and 0 otherwise yielding a maximum possible score of three.

Full descriptions of the tasks may be found in Hadjiefthyvoulou et al. (2011b).

Procedure

The tests were administered under laboratory conditions. The Ravens intelligence test was administered first followed by the age/education questionnaire. Next the F1 event based task was administered and instructions for the long-term time based task were provided. The fatigue short-term PM task was administered throughout the session and the drug use questionnaire was administered at the end. Participants were fully debriefed, given a 20 GBP supermarket (grocery store) gift card and given drug education leaflets. Participants also performed a range of other tasks that are beyond the scope of the present investigation.

Design and Statistics.

A between-participant design was used with drug user group (ecstasy/polydrug versus non-ecstasy user) as the independent variable. Dependent variables included all of the PM measures, i.e., the proportion of fatigue questionnaires completed during the first and second half of the test session, the number of times that participants forgot to press the F1 key for each of the three trials and the number of delayed recall tests participants remembered to mail back to the experimenter. Group differences were analysed via t test.

RESULTS AND DISCUSSION

Regarding background variables, inspection of Table 1 reveals that the two groups differed significantly in terms of age and the number of cigarettes consumed each day. Ecstasy/polydrug users were older and consumed more cigarettes. Furthermore, the ecstasy/polydrug group had a significantly higher level of lifetime cannabis use and a significantly shorter period of abstinence from the drug. Although ecstasy/polydrug users reported a higher current frequency of cannabis use, the difference was short of statistical significance. Ecstasy/polydrug users were significantly impaired on all but two of the PM

measures and on these remaining two, the difference approached statistical significance (see Table 1).

The present results replicate the findings from our previous study. Ecstasy/polydrug users made significantly more errors (forgetting to press F1) on each of the three trials of the event based task; they completed significantly fewer Karolinska fatigue questionnaires during both halves of the test session, with the deficit larger in magnitude during the second phase of testing; they also returned fewer delayed recall tests during the three weeks following the test session.

STUDY 2

Of the non-ecstasy users included in Study 1, over one third had used cannabis and 10% cocaine and the majority of these individuals appeared to be current users. Similar proportions were using these drugs among non-ecstasy users in our previous study. Since there is evidence to suggest that cannabis use is associated with self report (Fisk & Montgomery, 2008; Rogers et al. 2001) and laboratory based (McHale & Hunt, 2008; Montgomery, Seddon, Fisk, Murphy, & Jansari, 2012) PM deficits, the group difference evident in Study 1 and in our previous paper may actually underestimate the true difference between ecstasy/polydrug users and drug naïve individuals. Inclusion of a cannabis only user group and a group of nonusers of illicit drugs would clarify the nature of the ecstasy/polydrug related deficit and also allow us to directly test for group differences between cannabis-only users and nonusers of illicit drugs.

Most importantly, as outlined above, it has often not been possible to demonstrate clear long-term dose related effects of ecstasy and other illicit drugs on aspects of prospective memory. Rather than relying on single estimates of lifetime use, it may be useful to focus on other long-term aspects of use including the long-term dose (e.g., tablets, lines or joints

typically consumed per session) or the long-term frequency of use. Merging the sample from Study 1 with that of our previous study will create a sufficiently large sample in order to explore the associations between these long-term measures of illicit drug use and the PM outcomes. A larger sample size will help establish whether measures such as long-term average dose per session and frequency of use can explain variance in PM performance where more traditionally used measures of drug use such as total lifetime use, current frequency of use, period of abstinence, duration of use and average weekly long-term consumption may fail to reveal such a relationship.

METHOD

Participants.

One hundred and three ecstasy/polydrug users (51 females, 51 males, 1 not reported), 38 cannabis-only users (21 females), and 65 nonusers of illicit drugs (48 females) took part in this investigation (for demographic details see Table 2). The gender composition differed significantly between the groups with females predominating among the non illicit user group and a broadly even split among the cannabis only and ecstasy/polydrug users, $\chi 2\ (2) = 9.51$, $p<.01$. Participants, who were university students studying in the United Kingdom, were recruited via direct approach.

In addition to the individuals included in Study 1, 69 of the participants included in the present study also took part in our earlier study where we have previously reported some of the laboratory PM results for these individuals. Merging the samples together allowed us to include a cannabis only user group and a group of non-users of illicit drugs (in Study 1 the non-ecstasy user group contained a substantial minority of cannabis users and a small number of cocaine users). It also enabled us to create sufficient numbers of illicit drug users so that long and short-term dose-related effects could be properly investigated. None of the present

merged sample reported use of ecstasy within the week prior to testing and none reported using any other illicit drug within the 24 hours prior to testing. All participants gave verbal consent and were tested in accordance with the national and local ethics guidelines and according to the Declaration of Helsinki.

Materials

The drug use and demographics questionnaires (and measures) were the same as those that featured in Study 1. In addition, in the present study, the historical annual estimates of typical dose per session and frequency of use for each year were considered separately and estimates of long-term dose (averaged over the number of years of use) and similarly the long-term average frequency of use were computed. This was done for each illicit drug that was regularly consumed.

Laboratory Measures of Prospective Memory

The same PM tasks were administered as in Study 1, that is, the F1 Short-Term Event Based Task, the Fatigue Short-Term Time Based Test, and the Mail Long-Term Time Based Test. Full descriptions of these may be found above.

Procedure

The procedure was the same as that outlined in Study 1.

Design/Statistics

A mixed design was used to analyse outcomes from the fatigue short-term time based PM task. The proportion of fatigue questionnaires completed in the first half and second halves of the test session were compared across the three participant groups

(ecstasy/polydrug, cannabis only, and non-illicit drug user). To explore any differences on the F1 event based PM task (omitting to press F1) a mixed design was again used. The number of errors was compared across three separate trials and between the three participant groups (ecstasy/polydrug, cannabis only, and non-illicit drug user). Responses from the mail long-term time based PM task were compared between the three user groups (ecstasy/polydrug, cannabis only, and non-illicit drug user) using a one way design. In all three analyses, gender and measures of current alcohol and cigarette use were included as covariates. With respect to the between participant comparisons, it was predicted, a priori, that non users would score significantly better than both cannabis only and ecstasy/polydrug users. For these two pairwise comparisons, an alpha value of .025, one-tailed, was selected. No prediction was made regarding the difference between the two drug using groups.

For those individuals using illicit drugs, associations between indicators of long and short-term drug use and the outcomes on the PM measures were investigated using correlation. It was predicted that increasing levels of illicit drug use would be associated with poorer PM performance and that PM performance would be positively associated with the period of abstinence.

While some means of controlling the Type 1 error rate is required it is now well established that full Bonferroni correction greatly inflates the likelihood of Type 2 error (Rothman, 1990). Where test results are conditionally dependent, (as is the case with the present study, where there are multiple interrelated outcome variables and multiple inter-correlated drug use measures) full Bonferroni correction is known to be inappropriate (Bland & Altman, 1995; Narum, 2006; Pike, 2010). Thus an alternative to full Bonferroni correction has been adopted here, which focusses on controlling the False Discovery Rate (FDR), a technique which is well suited to situations where the reported outcomes are not independent (Benjamini & Yekutieli, 2001). This involves controlling the proportion of occasions where

true null hypotheses are falsely rejected giving rise to ‘false discoveries’. Computational methods are available for calculating the critical value for alpha (also known as the q value) which controls the FDR at a given level (e.g., Pike, 2010). The FDR rate in the present study was set to .10 which implies that the proportion of significant outcomes which are actually false discoveries is limited no more than 10%. In fact, in the present case, significant outcomes that were not in the predicted direction are also rejected which effectively reduces the FDR to .05. There is a related procedure for calculating the critical alpha value which limits the Family Wise Error rate (FWE) to .05 without greatly inflating the risk of a Type 2 error, as is the case with full Bonferroni correction (Benjamini & Yekutieli, 2001; Narum, 2006). It is this critical level and the related FDR which has been used to identify those outcomes in Tables 4 and 5 which can be regarded as statistically significant with the FWE <.05 and FDR<.10, two tailed.

RESULTS

Group differences on the background variables are set out in Table 2.

Ecstasy/polydrug users were significantly older than nonusers. Both illicit drug using groups consumed significantly more units of alcohol per week than nonusers. Ecstasy/polydrug users smoked significantly more cigarettes each day compared with cannabis only and nonusers. In terms of illicit drug use, aside from ecstasy, most ecstasy/polydrug users regularly consumed cannabis and two-thirds of the group were regular cocaine users (see Table 3). On virtually all of the cannabis use measures set out in Table 3 ecstasy/polydrug users registered significantly greater cannabis use compared to cannabis only users.

The F1 event based PM task.

Examination of Table 2 reveals that relative to the other two groups, ecstasy/polydrug users committed more errors on this task by failing to press F1 at the end of each 30 second period on each of the three trials. Cannabis only users and non-illicit drug users performed similarly on this task. ANCOVA was administered with gender, daily cigarette and weekly alcohol consumption as covariates. Mauchly's test of sphericity was statistically significant, $p<.001$, therefore Greenhouse-Geisser adjusted degrees of freedom have been used. The interaction between drug user group and trial was non significant, $F<1$. There was a significant effect of trial, $F(1.45,268.40)=7.97$, $p=.002$, $\eta_p^2 = .041$, and the groups differed significantly, $F(2,185) = 7.28$, $p=.001$, $\eta_p^2 = .073$. Pairwise comparisons revealed that ecstasy/polydrug users committed significantly more errors than drug naïve persons, and cannabis only users, $p<.001$ and $p=.008$ respectively. Drug naïve persons and cannabis only users did not differ significantly, $p>.05$. None of the covariates were statistically significant, $p>.19$, and homogeneity of regression was obtained in all three cases.

The fatigue short-term time based PM task. Inspection of Table 2 reveals that non illicit drug users did best, remembering to complete more fatigue questionnaires than the other two groups. Cannabis-only users performed worse than non illicit drug users but better than ecstasy users. ANCOVA with the same covariates included as in the previous analysis revealed a significant interaction between drug user group and test session, $F(2,184)=7.42$, $p=.001$, $\eta_p^2 = .075$. As is clear in Table 2, while both user groups performed worse than nonusers during the first half of the session, nonusers broadly maintained their performance in the second half while the performance of the drug using groups deteriorated further. For the sample as a whole, performance deteriorated between the first and second halves of the session, $F(1,184)=35.25$, $p<.001$, $\eta_p^2 = .161$. The overall group difference was significant,

$F(2,184)=25.43$, $p<.001$, $\eta_p^2 = .217$. Pairwise comparisons revealed that, overall, both user groups performed significantly worse than nonusers, $p<.001$ in both cases. Furthermore, the ecstasy/polydrug group performed significantly worse than cannabis only users, $p=.020$, one tailed. None of the covariates were statistically significant, $p>.20$, for alcohol and nicotine consumption, although gender approached significance as a covariate, $F(1,184)=3.84$, $p=.052$, $\eta_p^2 = .020$. Homogeneity of regression was obtained in all three cases.

The mail long-term time based PM task. As is clear from inspection of Table 2, non-illicit drug users remembered to return more delayed recall tests compared to the other two groups. Ecstasy/polydrug users again performed worse on this measure, with cannabis only users scoring in between. ANCOVA with the same three covariates failed to yield a statistically significant group difference, $F(2,185)= 2.06$, $p=.131$, $\eta_p^2 = .022$. However pairwise comparisons revealed that non illicit drug users scored significantly higher than ecstasy/polydrug users, $p=.023$ one-tailed. None of the other pairwise comparisons were statistically significant, $p>.05$. None of the covariates were statistically significant, $p>.45$, for gender and nicotine consumption, although alcohol consumption approached significance as a covariate, $F(1,185)=3.39$, $p=.067$, $\eta_p^2 = .018$. Homogeneity of regression was obtained in all three cases.

Associations between long-term drug use and PM. A key objective of the present paper was to examine the association between the various laboratory PM measures and the long-term average dose per session and long-term average frequency of use for ecstasy, cocaine and cannabis. The corresponding correlations are presented in Table 4. Inspection of Table 4 reveals that, without adjustment for multiple comparisons, the long-term average dose of ecstasy is significantly associated with all but one of the PM measures. Using Benjamini and

Yekutieli's (2001) procedure for controlling the FWE, four of the eight correlations are statistically significant at FWE < .05, and using a two tailed FDR<.10 with m=48, five of the correlations are significant. It is also apparent that prior to adjustment for multiple comparisons, the long-term average frequency of cannabis use was significantly associated with the two time based PM measures, however, only the association with the Fatigue short term measure remains significant after controlling the FWE and FDR at the levels indicated above.

Examination of the more traditional measures of illicit drug use set out in Table 5 shows that, prior to adjustment for multiple comparisons, a number of these were significantly associated with individual PM outcomes. The fatigue short term measure (during the first half of the test session) was significantly associated with five of the drug use variables, four relating to aspects of ecstasy use and one to cocaine. Similarly, F1 event based PM task performance in Trial 1 was significantly associated with five of the drug use variables, two relating to aspects of ecstasy use and three to cocaine. These account for most of the unadjusted significant outcomes in Table 5. However, it is important to note that following control of the FWE rate at less than .05 only two of these associations remained statistically significant. Furthermore controlling the FDR at 0.10, two tailed, left **none** of the associations statistically significant. Clearly both these methods for controlling Type 1 error are sensitive to the number of comparisons made (i.e., m=120 in Table 5). It might be argued that the number of comparisons should be treated separately for each aspect of drug use. FWE and FDR analyses were repeated on each separate block of 24 comparisons (i.e., m=24) and as with the full analysis in each case none of the outcomes achieved significance at a level which guaranteed FDR<.10. Similarly, for each separate block of 24 comparisons, only the same two correlations were such that FWE <.05, i.e., the association between total cocaine use and F1 event based PM performance in Trial 1 and between the average weekly

consumption of ecstasy and performance during the first half of the Fatigue short term time based PM task.

For the seven statistically significant associations listed in Table 4 with the two tailed FDR<.10, partial correlations were conducted controlling for the long term average dose and frequency of use of the other main illicit drugs. Thus, the association between the relevant PM measures and the long term average dose of ecstasy was estimated while controlling for long term average frequency of ecstasy, cannabis and cocaine use and long term average dose of cannabis and cocaine. Similarly the association between the relevant PM measures and the long term average frequency of cannabis use was estimated while controlling for the long term average frequency of ecstasy and cocaine use and long term average dose of ecstasy, cannabis and cocaine. The resulting partial correlations (df=53) between the long term average dose of ecstasy and respectively the fatigue time based total, and first half performances were -.267 and -.279, and between the long term average dose of ecstasy and respectively the F1 event based total, and Trial 3 outcomes were .269 and .290. These four remained significant with FDR<.10 (m=7, two tailed). However the remaining partial correlations between the long term average dose of ecstasy and F1 event based Trial 1 performance, i.e., .164, and between the long term average frequency of cannabis use and the fatigue time based total, and first half performance, respectively -.163, and -.169, were not significant at a level which controlled the FDR at less than .10. Furthermore, while these outcomes are informative none of the associations met the threshold for controlling the FWE at less than .05 two tailed (although on a one tailed basis one of the significant FDR outcomes met the FWE criterion, p=.016, and all of the remainder approached significance, $.02 \leq p \leq .025$, one tailed, compared with the critical value of .019).

General Discussion

The present findings are consistent with previous studies (Hadiefthyvoulou et al. 2011a; Heffernan et al. 2001a; Montgomery & Fisk, 2007; Rendell et al. 2007) and support the view that ecstasy/polydrug use is associated with deficits in short term time and event based PM and in long term time based PM. However, we demonstrate here that outcomes on both the event and time-based short term PM measures are significantly associated with long term differences in the average dose of ecstasy consumed in a single session. Furthermore, the inclusion of a cannabis-only group showed that while ecstasy/polydrug users performed significantly worse than non illicit drug users on the FI event based task, cannabis-only users did not, which therefore suggests that the deficit here is due to some characteristic of polydrug use unrelated to cannabis consumption.

Interestingly cannabis-only uses were impaired in short term time based PM relative to drug naïve persons suggesting a direct effect of cannabis on this aspect of PM functioning. Indeed, both user groups exhibited significant deficits relative to drug naïve persons on the Fatigue PM measure during the second half of the test session. Furthermore ecstasy/polydrug users were significantly impaired relative to cannabis-only users on this measure. It is also of interest to note that the long term average **frequency** of cannabis use (among illicit drug users as a whole) was significantly associated with performance on the Fatigue PM measure (although interestingly this was during the first half of the test session).

Almost 90% of ecstasy/polydrug users in the present study also used cannabis and approaching 80% used cocaine, thereby raising the possibility that the effects on PM performance that we observed may be due to any one of these three major drugs, or to cocktail effects associated with their joint consumption. The evidence set out in Tables 4 and 5 appears to suggest that it is the long term average dose of ecstasy which is linked to most of the PM deficits that have been observed in the present paper. This appears to share

statistically significant variance with most of the PM measures. Furthermore, when we controlled for the effects of cocaine and cannabis, the negative associations between the long term typical average dose of ecstasy (per session) and performance on two of the three PM measures remained statistically significant, at least at a two tailed FDR <.10.

A key aspect of the present results is the importance of the long term typical dose of ecstasy in a single session. This appears to be directly related to adverse outcomes on the PM measures. This finding may be a corollary of the development of tolerance. Indeed, it has been demonstrated that the subjective effects of taking ecstasy diminish quite rapidly, leading many users to progressively increase their dose so as to maintain the intensity of the experience. In an extensive review of the literature Parrott (2005) attributes tolerance to serotonergic neurotoxicity. Consistent with this proposition, animal studies in rodents and primates have demonstrated long term reductions in serotonin, its metabolite 5-HIAA and in serotonin axon densities (e.g., Commins et al. 1987; Hatzidimitriou, McCann & Ricuarte, 1999) and neuroimaging studies in regular ecstasy users have demonstrated reduced SERT densities across the neocortex, and clear evidence of serotonin axonal damage and grey matter loss (Cowan et al. 2003; Kish et al. 2010). The progressive degeneration of the serotonergic system means that there are fewer sites for the drug to operate on thereby requiring increasing amounts to achieve the same pharmacological reaction (Parrott, 2005). The development of tolerance would lead to progressively larger doses and many users may resort to periodic binging (i.e., ‘stacking’ or ‘boosting’) to maintain the intensity of the subjective experience.

If drug use continues unabated, long term, then the increasing individual doses associated with growing tolerance will necessarily give rise to increased lifetime exposure and thus long term average dose and lifetime use will be co-related. However, the relationship is not necessarily isomorphic. For example, in Verheyden, Henry and Curran’s

(2003) sample, a significant number had cut back their use of the drug for various reasons (e.g., financial, adverse physical effects, adverse effects on work or education or because of the reduced subjective effects). Furthermore, in Scholey et al's (2004) sample while 24% of heavy users (more than 100 occasions of use) reported normal doses of between 3-4 tablets and 14% doses of 4+ tablets, the majority were normally consuming between 1-2 tablets per session, the same as the majority of moderate and novice users. Thus long term trends in the typical dose per session may not always show a straight forward relationship with total lifetime use.

The exact mechanisms through which MDMA causes neurotoxicity remain unclear. Recent investigations have suggested a role for cortisol in the process. Parrott (2009) notes that, in laboratory studies, administration of MDMA stimulates the hypothalamo-pituitary-adrenal (HPA) axis resulting in increased plasma concentrations of cortisol. In a study examining salivary cortisol levels in ecstasy users, increases of up to 800% were observed in participants who were clubbing and on drug compared with baseline and compared with dancing while drug free (Parrott, Lock, Conner, Kissling & Thome, 2008). In another recent study, Wolff et al. (2012) evaluated cortisol levels pre and post clubbing. Interestingly, at baseline, cortisol levels were elevated in their sample compared with normal population and diurnal norms. Post clubbing, increases in cortisol levels were again more pronounced in clubbers who had consumed ecstasy relative to those who had not. Furthermore, genetically based differences in the efficiency of drug metabolism moderated this effect. Specifically, post clubbing increases in cortisol among the ecstasy users were largely limited to those with the two CYP2D6 phenotypes characterised by poor or intermediate metabolism. A second genetic influence was apparent, linked to the COMT genotype (Met/Met) that is associated with low activity drug metabolism. Those associated with this particular phenotype registered larger increases in cortisol post clubbing irrespective of whether they had taken MDMA.

Wolff et al (2012) observe that regular use of MDMA may lead to chronic HPA axis dysregulation particularly in those with a genetic makeup characterised by poor xenobiotic metabolism.

In turn, it is possible that MDMA induced, cortisol mediated, HPA axis dysregulation may be responsible for some of the cognitive deficits associated with ecstasy use. Cortisol is known to directly affect learning and memory as well as attentional processes in an inverted U shaped manner with too much or too little resulting in cognitive impairment. It is directly involved in regulating the activity of a number of neurotransmitters that are crucial in supporting prefrontal executive processes including dopamine. Furthermore, chronically elevated levels have been associated with atrophy in the striatum, hippocampus and prefrontal cortex (Erickson, Drevets & Schulkin, 2003).

Whether ecstasy's neurotoxic effects are directly associated with MDMA, its metabolites, or produced indirectly via the effects on cortisol, it is of interest to consider which of the neural areas associated with PM performance may be susceptible to the drug. Over the previous several years much has been learned as to the neural basis of PM performance. In early neuroimaging research it was demonstrated that increased activity in the lateral frontopolar region, Brodmann area (BA) 10, was associated with retaining the PM intention, while, when the cue was detected, activity in medial BA 10 appeared to decline as attention was diverted away from the external ongoing task and the focus was switched to the internal representation of the PM intention (Burgess, Quayle & Frith, 2001; Burgess et al. 2003). Later research has demonstrated the involvement of other cortical and subcortical areas. During the storage phase, in addition to lateral BA10, activity is also higher in the bilateral medial frontal gyrus (BA 8/32), the left precuneus and left parietal cortex (BA7) (Benoit, Gilbert, Frith, & Burgess, 2012), as well as a region in BA46 extending to the insular cortex and the anterior cingulate (Gilbert, 2011). Responding to the cue and retrieving the

intention also results in increased activity in the VLPFC and lateral parietal cortex, the anterior cingulate, more superior regions of the DLPFC, as well as the orbitofrontal cortex (OFC) (Simons, Schölvinck, Gilbert, Frith & Burgess, 2006). Findings reported by Gilbert (2011) suggest that the specific content of the PM intention and the characteristics of the PM cue are not actually stored in BA10 but rather are reflected in differential activation elsewhere in both cortical (e.g., the medial rostral prefrontal and right superior parietal cortices, the medial occipital cortex) and subcortical structures (e.g., thalamus, putamen).

It is known that ecstasy damages axonal tissue though out much of the neocortex and it may be that one or more of the above mentioned neural areas may be particularly sensitive to ecstasy-related effects. The acute effects of ecstasy on PM were investigated in Ramaekers Kuypers, Wingen, Heinecke and Formisano's (2009) study in which participants, who were regular ecstasy users, performed an event based PM task. While performing the ongoing task and retaining the PM intention, fMRI revealed that relative to placebo, the BOLD response was reduced following the administration of MDMA in the left thalamus, left putamen, left precuneus (BA7), the left inferior /superior parietal lobule (BA40/7) and right inferior parietal lobule (BA40). When retrieving the PM intention administration of MDMA reduced the BOLD response in the inferior parietal lobe (bilateral BA40). Clearly many of the regions demonstrating acute MDMA sensitivity are the same as those supporting event based PM processing, e.g., the parietal cortex, the thalamus and putamen, and it may be that the same regions are implicated with respect to PM deficits in currently abstinent ecstasy/polydrug users.

Since the ecstasy/polydrug users in the present study were also impaired in time based PM, it is of interest to consider which neural areas might be implicated in this regard. Okuda et al. (2007) demonstrated that the lateral frontopolar cortex is also active in storing the intention in time based PM, although there were slight differences, with the left superior

frontal gyrus (BA9/10) more active in time based PM. Relative to event based PM, using a clock, instead of subjective time estimation, was associated with greater activation in the right superior frontal gyrus (BA10), the medial frontal lobe (BA10) and the adjoining anterior cingulate gyrus (BA32/10). In a later study, Momennejad and Haynes (2012) focussed on the specific content of the PM intention showing that, during retention, this was encoded in a range of medial PFC regions including BA 9/ 10, as well as left lateral BA 6, and the occipital lobe (BA17, right inferior BA19) . Differences in the specific timing of the PM intention appeared to be encoded in the lateral PFC including bilateral BA10, right BA46, and BA6, as well as right medial BA10, right posterior parietal lobe, right superior parietal cortex, and the anterior cingulate. At the point of retrieval different delays were associated with differential activation in additional regions including the right precuneus, the inferior right PFC (BA45) and orbitofrontal cortex (BA47).

The neuroimaging results have been augmented by clinical and lesion studies. For example, in a study of patients with focal brain lesions, following appropriate controls, right polar prefrontal (BA10) lesions were associated with a deficit in time-based PM while event-based PM performance was unrelated to lesion status. Interestingly, patients with frontopolar lesions were also significantly impaired in time estimation ability compared to other patients (Volle, Gonen-Yaacovi, de Lacy Costello, Gilbert, & Burgess, 2011). In another study, the relationship between PM performance and grey matter volumes in the medial temporal, prefrontal and parietal regions was examined in a sample of normal and mildly demented older adults. A significant positive association was apparent between medial temporal and more specifically hippocampal grey matter and performance on a focal PM task (Gordon, Shelton, Bugg, McDaniel, & Head, 2011). Lastly, Kondo et al. (2010) administered diffusion tensor imaging (DTI) on subjects with diffuse axonal injury, revealing a significant association emerged between PM performance and the degree of fractional anisotropy (an

indication of axonal damage) , in the left parahippocampal gyrus, left inferior parietal lobe, and left anterior cingulate.

Given the range of neural areas which appear to support time based PM processes, it is of interest to consider which of these may feature in the ecstasy-related deficits that have been observed here. Cowan et al. (2003) assessed regional brain grey and white matter concentration in ecstasy users and controls. The former had decreased grey matter in several brain regions, which were localised to the neocortex in bilateral occipital cortex (BA 18), left middle temporal gyrus (BA 21) and left inferior frontal gyrus (BA 45). Kish et al. (2010) investigated differences between ecstasy users and controls in serotonin transporter densities, the regional volume of grey and white matter and cortical thickness in particular ROIs. Consistent with the outcomes of previous studies (e.g., Buchert et al. 2004; Thomasius et al. 2006) the results revealed that SERT densities were significantly reduced in all cortical areas with the occipital and temporal cortices most affected. No significant differences in SERT binding emerged in the basal ganglia structures or the thalamus. Cortical thinning was evident especially in left hemisphere locations including the superior (BA6) middle (BA10 and BA9) and inferior (BA47) frontal gyri, inferior parietal (BA40), middle temporal gyrus (BA22), occipital cortex (BA17) and right inferior parietal. Furthermore the neural deficits evident in ecstasy/polydrug users were associated with aspects of prior ecstasy consumption (Kish et al. 2010).

Combining, the evidence set out above concerning the neural basis of PM performance and what is known regarding neural damage in ecstasy users, one clear area that is implicated is the frontopolar cortex (lateral BA10) which plays a crucial role in both time and event based PM (e.g., Gilbert, 2011; Okuda et al. 2007) and which has been to shown to exhibit reduced SERT densities and cortical thinning in ecstasy/polydrug users (e.g., Kish et al, 2010). Indeed as noted above patients with right polar prefrontal BA10 lesions were

shown to be impaired in time based PM (Volle et al. 2011). It is also possible that the DLPFC more generally (including BA6 BA9) may similarly be implicated. Also the parietal cortex cannot be excluded since it has been identified as playing a role in time and event based PM and also exhibited reduced SERT densities and cortical thinning in Kish et al's (2010) study. Furthermore, reduced activity in areas of the parietal cortex, following acute MDMA administration, was shown to be directly associated with impaired PM performance (Ramaekers et al. 2009).

A number of limitations need to be acknowledged in relation to the present study. In common with much of the existing literature, this study has relied on self-report data in relation to drug use. However, while objective measures would have been desirable, research suggests a high degree of concordance between self-report and objective measures of recent drug use from saliva (Yacoubian & Wish, 2006) and of longer term use from hair (Scholey et al. 2011; Vignali, Stramesi, Vecchio, Groppi, 2012). Furthermore, concordance between self-reports and objective measures of drug use has been demonstrated for multiple illicit drugs (Vignali et al. 2012), cannabis and cocaine (Vignali et al. 2012; Zaldívar et al. 2009) and ecstasy (Scholey et al. 2011; Yacoubian & Wish, 2006). Obviously it neither ethical nor feasible to administer MDMA to humans for prolonged periods so we have used an opportunity sample. Clearly we cannot exclude the possibility that our groups differed on some other pre-existing condition predating their drug use or in terms of some other lifestyle variable. While we have attempted to control for a number of potential confounds, there may be others perhaps as yet unknown which may have had an impact on the results reported here. In conclusion, the present study has identified clear long-term **dose**-related effects of ecstasy use on PM performance and in doing so has furthered the current understanding of the basis of PM deficits among ecstasy users. Outside the laboratory, the results obtained may also

have utility in informing the development of harm reduction interventions by highlighting the potential risks associated with taking large number of tablets in a single session.

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Table 1: Demographic Variables, Prospective Memory Outcomes and Drug Use Indicators: Study 1

	Ecstasy/Polydrug Users			Non-ecstasy Users			p
	Mean	SD	n	Mean	SD	n	
Age	21.91	2.40	64	20.89	2.38	85	.012
Ravens progressive matrices (maximum 60)	43.95	7.80	62	45.26	8.13	82	ns
Years of education	16.15	1.67	56	15.82	1.90	78	ns
Alcohol (units per week)	13.85	10.47	62	12.49	11.85	75	ns
Cigarettes per day	3.61	4.58	65	1.15	3.44	85	<.001
Fatigue: Short-term time based PM (%)							
Total	54.33	28.39	65	71.40	25.30	82	<.001
First Half	70.26	30.96	65	79.82	29.07	82	(.056)
Second Half	38.87	34.27	65	62.99	35.21	82	<.001
Mail: Long-term time based PM	0.89	1.23	65	1.39	1.35	84	.021
F1: Event based PM							
Total	1.77	2.83	64	0.71	1.48	85	.004
Trial 1	0.78	1.19	64	0.46	0.96	85	(.069)
Trial 2	0.53	1.11	64	0.12	0.45	85	.002
Trial 3	0.45	0.97	64	0.13	0.57	85	.012
Total Prior Consumption							
Cannabis (joints)	1658.02	3162.11	52	485.65	1423.81	30	.024
Cocaine (lines)	616.90	994.41	43	54.28	81.97	4	
Ecstasy (tablets)	316.51	654.56	60	-	-	-	
Current Frequency of Use (times per week)							
Cannabis	2.46	8.60	55	0.43	1.25	35	ns
Cocaine	0.43	0.80	47	0.16	0.28	7	
Ecstasy	0.16	0.25	64	-	-	-	
Weeks since last use[a]							
Cannabis	31.05	56.87	57	78.47	106.37	37	.016
Cocaine	31.61	58.93	49	31.14	40.40	9	
Ecstasy	52.43	72.72	65	-	-	-	

a. The *median* period of abstinence from cannabis was 8 and 16 weeks for ecstasy/polydrug users and non-ecstasy users respectively. The equivalent figures for cocaine were 8 and 20 weeks. The median period of abstinence for ecstasy was 12 weeks.

Table 2: Demographic Variables, Current Consumption of Alcohol and Cigarettes and Prospective Memory Outcomes: Study 2

	Ecstasy/Polydrug Users			Cannabis only users			Nonusers			p value (two-tailed) for oneway ANOVA and Tukey's HSD			
										Overall	E/P vs Non	Cannvs Non	E/P vsCann
	Mean	SD	n	Mean	SD	n	Mean	SD	n				
Age	21.85	2.98	102	21.47	3.00	38	20.64	2.23	65	.024	.018		
Ravens progressive matrices (maximum 60)	44.00	8.99	99	45.71	7.04	38	44.78	8.31	63	ns			
Years of education	15.25	3.20	93	15.55	2.32	33	15.30	2.22	63	ns			
Alcohol (units per week)	14.44	10.32	99	13.66	11.48	35	8.19	10.20	59	.001	.001	.041	
Cigarettes per day	4.17	6.16	103	1.53	3.17	38	0.98	3.63	65	<.001	<.001		.016
Fatigue: Short-term time based PM (%)													
Total	47.37	28.47	103	61.07	23.44	36	77.15	22.05	64	<.001	<.001	.009	.018
First Half	63.41	34.15	103	72.13	30.88	36	84.63	22.88	64	<.001	<.001		
Second Half	28.40	32.08	103	44.31	37.80	36	69.80	32.40	64	<.001	<.001	.001	.038
Mail: Long-term time based PM	0.86	1.21	103	1.18	1.23	38	1.58	1.32	64	.002	.001		
F1: Event based PM													
Total	1.75	2.74	102	0.74	1.11	38	0.60	1.48	65	.001	.003		.037
Trial 1	0.82	1.20	102	0.61	1.00	38	0.38	0.91	65	.038	.030		
Trial 2	0.50	1.09	102	0.05	0.23	38	0.08	0.41	65	.001	.003		.011
Trial 3	0.43	0.96	102	0.08	0.27	38	0.14	0.63	65	.015	.048		.046

Table 3: Measures of Illicit Drug Use for Ecstasy/Polydrug and Cannabis-Only Users: Study 2

	Ecstasy/Polydrug User				Cannabis Only User				p
	Median	Mean	SD	n	Median	Mean	SD	n	
Long-Term Average Dose Per Session									
Cannabis (joints)	2.20	2.71	1.89	85	1.00	1.36	0.88	31	<.001
Cocaine (lines)	4.83	6.49	6.53	64	-	-	-	-	
Ecstasy (tablets)	2.00	2.95	3.80	97	-	-	-	-	
Long-Term Average Frequency (times per week)									
Cannabis	1.00	1.74	2.07	85	0.23	1.02	1.69	31	.084
Cocaine	0.23	0.52	0.66	64	-	-	-	-	
Ecstasy	0.23	0.54	0.91	97	-	-	-	-	
Total Prior Consumption									
Cannabis (joints)	442.00	2110.56	3646.62	85	23.92	473.10	1404.83	31	.001
Cocaine (lines)	247.52	695.78	1113.89	64	-	-	-	-	
Ecstasy (tablets)	63.44	420.28	887.38	97	-	-	-	-	
Average weekly consumption									
Cannabis (joints)	2.04	7.98	11.69	87	0.68	2.47	4.71	30	<.001
Cocaine (lines)	2.17	28.99	164.11	63	-	-	-	-	
Ecstasy (tablets)	1.16	2.55	3.67	95	-	-	-	-	
Duration of use (weeks)									
Cannabis	264.00	297.06	192.80	91	108.00	180.35	199.27	37	.003
Cocaine	127.57	159.96	124.93	75	-	-	-	-	
Ecstasy	133.50	160.48	139.92	102	-	-	-	-	
Current Frequency of Use (times per week)									
Cannabis	0.24	1.86	6.81	90	0.01	0.53	1.45	36	.249
Cocaine	0.14	0.43	0.72	70	-	-	-	-	
Ecstasy	0.04	0.17	0.26	102	-	-	-	-	
Weeks since last use									
Cannabis	4.00	32.07	63.72	92	24.00	77.35	92.57	37	.009
Cocaine	8.00	29.86	59.21	77	-	-	-	-	
Ecstasy	12.00	45.93	70.59	103	-	-	-	-	

Table 4: Association between Long Term Average Dose and Frequency of Use of Major Illicit Drugs and Prospective Memory Outcomes

	n	Zero-Order Correlation with:							
		Fatigue: Short-term Time-based PM			Mail: Long-term time-based PM	F1: Event-based PM			
		Total	First Half	Second Half		Total	Trial 1	Trial 2	Trial 3
Long-Term Average Dose Per Session									
Cannabis (joints)	123	-.141	-.131	-.121	-.066	.120	.074	.139	.086
Cocaine (lines)	70	-.260**	-.195	-.229*	.092	.006	.225*	-.115	-.112
Ecstasy (tablets)	96	-.300***†	-.320***†	-.183*	-.158	.295***†	.249**†	.232**	.268***†
Long-Term Average Frequency (times per week)									
Cannabis	123	-.246***†	-.256***†	-.141	-.151*	.109	.071	.115	.085
Cocaine	70	-.089	-.141	-.074	.029	.163	.149	.148	.119
Ecstasy	96	-.117	-.140	-.034	-.008	.096	.139	.054	.039

*p<.10; **p<.05; *** p< .01121 and FWE <.05 ; †FDR<.10 with m=48; all two tailed

Table 5: Association between More Commonly Used Measures of Illicit Drug Use and Prospective Memory Outcomes

	n	Zero-Order Correlation with:							
		Fatigue: Short-term Time-based PM			Mail: Long-term time-based PM	F1: Event-based PM			
		Total	First Half	Second Half		Total	Trial 1	Trial 2	Trial 3
Total Prior Consumption									
Cannabis (joints)	123	-.128	-.104	-.126	-.079	.038	.008	.041	.051
Cocaine (lines)	70	-.072	-.045	-.129	.120	.083	**.330*** **	-.073	-.066
Ecstasy (tablets)	96	-.182	-.213**	-.075	-.090	.206	.189*	.166	.166
Average weekly consumption									
Cannabis (joints)	125	-.191	-.171*	-.123	-.160*	.032	.000	.069	.012
Cocaine (lines)	69	-.063	-.092	.005	-.076	-.087	-.082	-.069	-.071
Ecstasy (tablets)	94	-.234	**-.278*** **	-.101	-.065	.195	.176*	.151	.172*
Duration of use (weeks)									
Cannabis	136	-.097	-.036	-.145*	-.029	.069	.040	.087	.043
Cocaine	85	-.062	-.073	-.105	-.059	.161	.232**	.152	.014
Ecstasy	101	-.014	-.015	-.018	-.006	.019	.026	.050	-.036
Current Frequency of Use (times per week)									
Cannabis	133	.125	.064	.154(*)	.105	.046	-.033	.047	.128
Cocaine	78	.081	-.012	.144	-.067	.033	.196*	-.061	-.071
Ecstasy	101	-.192	-.170*	-.152	-.049	.149	.065	.182*	.139
Weeks since last use									
Cannabis	137	.155	.128	.084	-.058	-.184	-.137	-.170**	-.142*
Cocaine	88	.150	.225**	.073	.024	-.131	-.092	-.116	-.132
Ecstasy	102	.120	.130	.076	-.178(*)	.093	.151	.030	.042

*p<.10; **p<.05; *** p< .00879 and FWE<.05; †FDR<.10 with m=120; all two tailed;

(*) indicates that although p<.10, the effect was not in the predicted direction

Temporal and visual source memory deficits among ecstasy/polydrug users.

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Running head: source memory deficits and illicit drug use.

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Abstract

Objectives: The present paper seeks to investigate whether source memory judgements are adversely affected by recreational illicit drug use.

Method: Sixty-two ecstasy/polydrug users and 75 non ecstasy users completed a source memory task, in which they tried to determine whether or not a word had been previously presented and if so, attempted to recall the format, location and temporal position in which the word had occurred.

Results: While not differing in terms of the number of hits and false positive responses, ecstasy/polydrug users adopted a more liberal decision criterion when judging if a word had been presented previously. With regard to source memory, users were less able to determine the format in which words had been presented (upper versus lower case). Female users did worse than female nonusers in determining which list (first or second) a word was from. Unexpectedly, the current frequency of cocaine use was negative associated with list and case source memory performance.

Conclusions: Given the role that source memory plays in everyday cognition, those who use cocaine more frequently might have more difficulty in everyday tasks such as recalling the sources of crucial information or making use of contextual information as an aid to learning.

Key words: source memory, context memory, MDMA, cocaine, SDT sensitivity

INTRODUCTION

The purpose of the present paper is to investigate the integrity of source memory processes in recreational ecstasy/polydrug users. Source memory is concerned with the ability to recall the contextual and other episodic details in which a specific behaviour, idea or event occurs or a stimulus is encountered, for example, where a specific piece of information was originally encountered, in which particular shop a desired product had previously been seen or what time a specific medication was last taken. Source memory judgement may also involve distinguishing between external sources, i.e., determining which particular person was the source of a specific piece of information. Also distinguishing between internal sources, e.g., whether a particular course of action was actually carried out or just considered. Source memory also involves the ability to retrieve relevant contextual information (perceptual, spatial, temporal, semantic and affective) that was associated with a particular item or behaviour at encoding (Johnson et al. 1993). This may involve recalling which particular person was responsible for providing a particular piece of information and perhaps the time and context in which it was provided. In that sense source memory is a multidimensional phenomenon in that multiple and qualitatively different aspects of the context are encoded and potentially retained along with the actual information itself.

Depending on the conditions at encoding (motivational factors, the time available, the level distraction and the integrity of attentional processes) in some instances this process may result in rich source information in which multiple contextual attributes can be retrieved while in other cases relatively little source detail may be available (Johnson et al. 1993). It is also the case that some source information can be retrieved automatically and effortlessly along with the content of the memory at the point of recollection while in other situations the

contextual and perceptual characteristics of the item recalled are not immediately available and have to be actively reconstructed often through a process of deduction (Johnson & Raye, 1981).

Despite its multidimensional nature, experimental paradigms typically focus on single contextual dimensions such as whether a word was presented by a male or female voice (Lindsay et al, 1991), or at the right or left hand side of a computer display (Johnson et al, 1982) or the colour in which the word was presented (Chalfonte & Johnson, 1996). Recalling whether or not a particular word was previously presented is referred to as item memory. Recalling the context in which that word was presented (e.g., as part of the first or second list, in red or green, at the top or bottom of the screen, or auditory features such as male or female voice) is characterised as source memory.

Source memory is known to play a vital role in everyday life. For example, the ability to accurately recall the source of some piece of crucial information and more importantly its veracity, is potentially of critical importance in everyday decision making (Johnson et al. 1993). The physical or temporal context in which objects or ideas are experienced frequently act as an aid to recall when these elements need to be retrieved. Indeed, in terms of the general acquisition of knowledge and factual information, research has shown that a positive relationship exists between the level of comprehension achieved and the ability to recall the source of the information that has been learned (Strømsø et al. 2012). Furthermore, misattributing the source of information, for example the mistaken belief that a person that you have encountered in one context was the actual protagonist in another, may have serious consequences and has been a factor in compromising the value of eye-witness testimony (Davis and Loftus, 2007; Zaragoza and Lane, 1994). There is clear evidence from studies of clinical populations, e.g., persons with brain injury, those with dementia or psychoses, of the

severe consequences which emerge when source memory is impaired (Mitchell and Johnson, 2009).

There is now a considerable body of evidence for the separable nature of item and source memory. For example the latter has been shown to deteriorate faster as a consequence of cognitive ageing (Kausler & Puckett 1980; 1981; Burke & Light, 1981; Ferguson et al. 1992) or with the progression of dementia (Multhaup & Balota, 1997) and the recollection of the source of information has been found to be differentially impaired in patients with frontal lobe lesions (Shimamura, 2002). The neural basis of source and item memory has also been extensively studied. For example, neuroimaging evidence suggests that, relative to item memory judgements, source memory results in greater activation in left hemisphere pre-frontal cortical structures (Kahn et al. 2004; Mitchell et al. 2008). Source memory can also have a temporal dimension and in common with other types of source memory judgements, paradigms involving temporal judgements, for example, identifying which of two ***temporally*** separated lists targets were from, also recruit left hemisphere PFC structures but also other cortical regions including the right hemisphere PFC and the orbito-frontal cortex (OFC) (Duarte et al. 2010). Thus item and source memory and indeed different types of source memory judgements appear recruit qualitatively different prefrontal resources again consistent with the separability of the two constructs. Lastly, experimental manipulations which have been found to enhance source memory performance have been found to have no effect on item memory, while manipulations which improve recognition have been found to actually hamper source memory (Lindsay & Johnson, 1991).

Meta analytic studies have suggested that ecstasy/polydrug users perform significantly worse on a number of executive sub processes that are known to rely on prefrontal cortical resources. This has been demonstrated both in relation to verbal (Murphy et al. 2009; Nulsen et al. 2010) and visuo-spatial processing (Murphy et al. 2012). Regarding

item memory, a number of researchers have found that ecstasy/polydrug users perform worse on the Rey Auditory Verbal Learning Test (RAVLT) (e.g., Bedi & Redman, 2008; Schilt et al. 2008). While there has been a considerable degree of controversy concerning the causes of the performance decrements that have been observed, it has been argued that they are at least in part attributable to ecstasy use (e.g., Parrott, 2013). In view of the importance of effective source memory processes for everyday functioning, and given that ecstasy/polydrug users have been observed to perform worse on various tasks which appear to recruit the same prefrontal and medial-temporal cortical resources that support source memory, it would be of value to establish whether or not individuals with a history of illicit drug use were less competent in terms of their source memory performance.

It is predicted that ecstasy/polydrug users will produce fewer correct source memory judgements relative to non ecstasy users. In view of the prevalence of polydrug use among ecstasy users, source memory performance will be correlated with various measures of illicit drug use. It is predicted that source memory performance will be negatively associated with the amount of ecstasy consumed and the frequency of use.

METHOD

Participants

Sixty-two ecstasy/polydrug users (including 37 males, 25 females) and 75 non ecstasy using controls (including 27 males, 48 females) from universities in the North West of England participated in the study. The control group included drug naïve, cannabis only and some cocaine users. Potential participants responded to advertisements placed around campus and via an on-line participant panel. They were initially informed that the study was concerned with the effects of illicit drugs on aspects of cognitive functioning and that both users and nonusers of illicit drugs could participate. Those with current or previous

psychiatric diagnosis or treatment (including flashbacks, panic attacks, paranoia, schizophrenia, phobia) were excluded from the study (see Bedi & Redman, 2008). Although details of ethnic origin were not recorded, the sample consisted predominantly of 'White British'. Participants were asked to abstain from cannabis use for at least 24 hours prior to testing and from other illicit drugs for at least 7 days prior to testing.

Materials

The use of ecstasy and other drugs was assessed by means of a self-report questionnaire. For all illicit drugs that were regularly consumed, participants estimated their typical dose and frequency of use for each year since they began using. This allowed the long term average dose per session and total lifetime use for each drug to be estimated. Participants also indicated their current frequency of use and period of abstinence Current use of alcohol and cigarettes and demographic variables including age and gender were also recorded and fluid intelligence was measured through Raven's Progressive Matrices (Raven et al. 1998).

Source Memory Task: The task was based on paradigm developed by Meiser and Broder (2002). Participants were asked to make judgements as to the spatial location, temporal order and format (upper versus lower case) of previously presented words. These types of judgement are commonplace in source memory research (see Meiser & Broder, 2002 for a summary of the relevant research). More specifically, 64 words (one or two syllable nouns) were presented each for 4 seconds on a computer monitor. Thirty two words were presented in List One and 32 in List Two. For each list, half the words were presented in the top section and half in bottom section of the computer monitor. For each of the resulting four sets, each word was presented in either upper or lower case. Words were randomly assigned to each list. Case and position were also determined in a quasi-random manner subject to the

requirement that each list had 16 words in upper case of which eight were presented in the top and eight at the bottom of the screen and 16 words in lower case again with eight presented at the top and 8 at the bottom of the screen. In the recognition phase all 64 words were presented with 64 new words.

Participants were asked to indicate (by pressing one of two computer keys) whether each presented word had been seen previously and if so to whether it was in the top or bottom half of the screen, in upper or lower case, and in list one or list two. In terms of item memory, the data recorded included the number of hits (previously seen words correctly identified), the number of false positive responses (new words mistakenly identified as previously seen), an estimate of sensitivity as defined in Signal Detection Theory (SDT), i.e., $z(H) - z(F)$ (where H is defined as the proportion of correct responses and F the proportion of false positive responses) and SDT decision criterion, i.e., $-[z(H) + z(F)] /2$ (Green & Swets, 1974). In relation to source memory, for those previously presented words that were correctly identified (hits), the percentage of correct source memory judgements was calculated with respect to list (first or second), position (top or bottom) and case (upper or lower).

Procedure

The research was approved by the Ethics Committees of the University of Central Lancashire and Liverpool John Moores University and was conducted in accordance with the requirements of the Declaration of Helsinki except that participants provided **verbal** consent in order to protect the anonymity of the illicit drug users in the sample. The tests were administered in the following order: background drug use questionnaire, Ravens Progressive Matrices and the source memory task. A number of other measures was also administered the results of which are outside the scope of the present study. These included tests of prospective memory and associative learning. In total the test battery took between two and

three hours to administer. At the end of the session, participants were debriefed, paid 20 UK pounds in the form of a supermarket (grocery store) gift card, and provided with drug education leaflets.

Design and Statistics

A between groups design was used with ecstasy use (ecstasy/polydrug users versus non ecstasy users) and gender between participants. Gender was included in order to establish whether any group related effects were consistent between males and females. Dependent variables were the proportions of correct position, list, and case **source** memory judgements. Regarding item memory, dependent variables were the SDT sensitivity and decision criterion values and the number of hits and false positive responses. Correlations between various indicators of illicit drug use and the source and item memory outcome measures were also explored.

RESULTS

Inspection of Table 1 reveals that the two groups did not differ significantly on most of the background measures. Ecstasy/polydrug users were slightly but significantly older and had significantly more years of education. Although cannabis use was generally more prevalent among the ecstasy/polydrug users, the two groups did not differ significantly on the majority of measures. By way of exception, in relation to period of abstinence, non-ecstasy users were abstinent from cannabis for significantly longer. There was also a significant interaction between gender and group with male ecstasy/polydrug users having a larger long term average dose of cannabis per session compared to the other three groups (see Table 2).

<Insert Tables 1 and 2 about here>

In relation to the item and source memory results, inspection of Table 3 reveals that ecstasy users performed worse than controls on the majority of measures. Specifically male ecstasy users achieved the smallest proportion of correct position and case source memory judgements; female ecstasy users achieved the smallest proportion of correct list source memory judgements. Male ecstasy users recorded the greatest number of false positives, they exhibited the lowest level of sensitivity and the most liberal decision criterion.

<Insert Table 3 about here>

A series of ANOVAs were conducted with group (ecstasy/polydrug versus non-ecstasy user) and gender between participants. Regarding the item memory outcomes, neither of the group effects or the interactions were statistically for hits and false positive responses, $F<1$, in all cases (except for the effect of gender on hits, $F=2.18$, $p=.143$, $\eta_p^2=.016$, and false positive responses, $F=2.62$, $p=.108$, $\eta_p^2=.019$, and the effect of user group on false positive responses, $F=2.74$, $p=.100$, $\eta_p^2=.020$) all on 1,133 DF. The ecstasy/polydrug-related effect for the SDT sensitivity measure was statistically significant, $F=4.01$, $p=.047$, $\eta_p^2=.031$, users exhibited lower levels of sensitivity. The gender effect and the interaction were not significant, $F<1$ in both cases; all on 1,124 DF. There was a significant effect of gender for the SDT decision criterion measure, $F=5.55$, $p=.020$, $\eta_p^2=.043$, females adopted a more stringent decision criterion. The drug related group effect and the interaction were not significant, $F=1.05$, $p=.307$, $\eta_p^2=.008$, and $F<1$ respectively; all on 1,124 DF.

Considering the source memory outcomes, on the list measure, the gender effect was non-significant, $F<1$, as was the overall group effect, $F=1.73$, $p=.191$, $\eta_p^2=.013$. However, there was a significant interaction between group and gender, $F=3.99$, $p=.048$, $\eta_p^2=.029$. The trends in the cell means are displayed in Figure 1. There was little difference in list memory performance between male users and nonusers. Female users registered the worst performance while female non ecstasy users achieved the best score. Post hoc tests revealed

that female users were significantly worse than female nonusers, p=.048, two tailed, but did not differ from either male users, or male nonusers, p>.05 in both cases. Regarding the other two source memory measures, the effect of group was statistically significant for case source memory F=5.40, p=.022, η_p^2 =.039. Users performed significantly worse when making case source memory judgements. The gender effect was also significant F=4.81, p=.030, η_p^2 =.035, with females performing better than males overall. The interaction was non-significant, F<1. For the position source memory judgement, neither the ecstasy/polydrug related effect, nor the interaction were statistically significant, F<1 in both cases. The gender effect approached significance, F=3.25, p=.074, η_p^2 =.024, with females performing better than males overall. All the above mentioned source memory effects were on 1,133 DF.

The association between aspects of illicit drug use and the source memory outcomes are set out in Table 4. Where test results and the probabilities associated with them are conditionally dependent, (as is the case with the present study, where there are multiple interrelated outcome variables and multiple inter-correlated drug use measures) full Bonferroni correction greatly inflates the likelihood of Type 2 error (e.g., Narum, 2006), so an alternative procedure (Benjamini and Yekutieli, 2001) which more effectively controls the Family Wise Error (FWE) rate was used. With 90 correlations reported in Table 4, an alpha value of .00942 controls the FWE <.05 two tailed (From Appendix A, Narum, 2006).

<Insert Table 4 about here>

On this criterion, the current frequency of cocaine use was significantly and negatively correlated with list source memory performance, p<.001, and the correlation approached significance for case source memory, p=013. Thus those with a higher current frequency of use had poorer source memory for whether the word was presented in list 1 or list 2 and for the case in which the word was presented. Period of abstinence from cocaine was significantly correlated with the position source memory component, p=.008, and the

correlation approached significance for case source memory (p=.0103). Thus as the period of abstinence from cocaine increased so source memory performance with respect to case and position improved. Contrary to expectation, only one of the indicators of ecstasy use was significantly associated with the memory outcomes at the adjusted alpha level: as the long term average dose of ecstasy per session increased, so list source memory deteriorated, p=.009.

Of those associations that were in the predicted direction, a further two were associated with p<.05, and three with p<.10, two tailed. For these, increased drug use and shorter periods of abstinence were associated with worse memory performance. In four instances the associations relate to source memory outcomes while the remaining case relates to the SDT D-Prime measure. Three are related to aspects of cocaine use, one to ecstasy and one to cannabis use. With one exception, none of the indicators of cannabis use were significantly associated with the source or item memory outcomes even at the unadjusted alpha level p=.10. The association between the total consumption of ecstasy and case source memory was not in the predicted direction with higher lifetime consumption associated with better case source memory and although not significant at the adjusted alpha level, p value was <.10 two tailed.

In view of the prevalence of cocaine use among the ecstasy users in the sample and vice versa, those zero order correlations that were statistically significant at p<.05 were repeated this time controlling for ecstasy or cocaine use as appropriate. The resulting partially correlations revealed that the current frequency of cocaine use remained significantly correlated with list and case source memory and the SDT sensitivity measure following controls for the frequency of ecstasy use, r_p(df=41) = -.535, p<.001; -.347, p<.05; and -.309, p<.05; respectively. Likewise the period of abstinence from cocaine remained significantly correlated with case source memory, r_p (df=43) = .414, p<.01, and the correlation with

position source memory approached significance, r_p (df=43) = .280, p=.063, following control for the period of abstinence from ecstasy. Finally the partial correlation between the long term average dose of ecstasy per session and list source memory remained statistically significant after controlling for the long term average dose of cocaine per session r_p (df=36) = .339, p<.05.

Inspection of Table 4 reveals that the use of cocaine within the previous 10 days was negatively correlated with list memory performance, p<.05. Similarly the period of abstinence from cocaine was positively associated with list memory performance, p<.10 and with case memory, p<.05. Although these associations were not significant at the adjusted alpha level, it is possible that some of the variance shared between the current frequency of use and, respectively, list and case memory, overlaps with the common variance shared with recent use within the previous 10 days and period of abstinence. In other words at least part of the significant relationship between current frequency of cocaine use and list and case memory might be attributable to very recent patterns in cocaine use. To evaluate this possibility a partial correlation was run between the current frequency of use and list memory, controlling for recent use within the last 10 days and period of abstinence. The relationship between current frequency and list memory remained statistically significant, r_p=-.490, d.f.= 45, p<.001. The equivalent partial correlation between case source memory and the current frequency of cocaine use also remained statistically significant (on an unadjusted basis) following the same controls, r_p=-.363, d.f.= 45, p<.05.

DISCUSSION

It is worthy of note that the performance of ecstasy/polydrug users did not differ significantly from nonusers in terms of three of the item memory measures, specifically they the groups did not differ significantly in terms of the number hits, false positive responses

and the SDT sensitivity measure. Users did appear to adopt a significantly more liberal decision criterion when judging whether or not a word had occurred previously, that is to say, they required less evidence or confirmatory information before making an affirmative response.

In relation to source memory, ecstasy/polydrug users did significantly worse relative to non-ecstasy users on case judgements. In the present context they were less able to recall whether a previously seen word was originally presented in upper or lower case letters. Assuming that the results can be applied to visual processing more generally, this supports the proposition that they are less able to recall the physical or visual form in which information is presented. In the present context list source memory reflected the ability to recall the temporal order in which words were presented. Female ecstasy/polydrug users registered the worst performance in this area while female non-ecstasy users achieved the best performance. The performance of males appeared to be unrelated to the ecstasy/polydrug user-nonuser distinction and was intermediate in magnitude. Lastly, the two groups did not differ in terms of the proportion of correct position source memory judgements which suggests that, at the group level, source memory for spatial location is unaffected by ecstasy/polydrug use.

With regard to the correlational analyses, only one aspect of ecstasy use, long term average dose per session, appeared to be significantly related to source memory performance. The typical dose per session (number of tablets typically consumed on each occasion of use) averaged over the entire period of use was found to be inversely related to source memory for temporal information. Lifetime use was not significantly associated with list memory. Thus it is the typical dose rather than total lifetime exposure which appears to be important. Evidence has emerged from structural and functional MRI studies of currently abstinent ecstasy/polydrug users, linking reduced SERT distribution volume ratios (DVRs) with

maximum and typical ecstasy dose per session (Kish et al., 2010; McCann et al., 2005, 2008; Thomasius et al., 2006). Thus, it could be that higher ecstasy doses give rise to source memory deficits as a consequence of their detrimental effect on SERT DVRs. Nonetheless such a possibility needs to be treated with a degree of caution since there is no obvious reason why this particular aspect of source memory should be particularly susceptible to the effects of ecstasy and it is worthy of note that the association between total lifetime use and case source memory was actually positive, (although at $p<.10$ two tailed, given the directional nature of the prediction this aberrant result is below significance even at an unadjusted alpha level).

Among the illicit drug users tested here it appears that cocaine use was associated with adverse outcomes on a number of the source and item memory measures. The current frequency of cocaine use was found to be significantly correlated with temporal source memory (the list measure) and, on an unadjusted basis, with source memory for presentation format (the case measure). In both cases higher frequency of use was associated with worse performance. Furthermore, it appears that the magnitude of the source memory deficit declines as the period of abstinence from cocaine increases. This was true for source memory for spatial position (the position measure) and, on an unadjusted basis, for presentation format source memory (the case measure). While the deficit was apparently related to the frequency with which cocaine was used, the effects observed do not appear to relate to recent use since the source and item memory outcomes either appear unrelated to recent cocaine use or the current frequency effect observed remains significant following statistical control for aspects of recent use. Three of the other measures of cocaine use were associated with various source and item memory outcomes at $p<.05$ or $p<.10$ two tailed although these failed to reach significance at the adjusted alpha level. As far as the authors are aware the present study is the first to link recreational use of cocaine with source memory deficits.

Regarding the apparent cocaine-related effect reported here and given the reliance of source memory performance on executive processes, it is worthy of note that, in previous research, performance deficits on a number of executive function tasks have been observed among currently abstinent cocaine users (Berry et al. 1993; Rosselli et al. 2001; Beatty et al. 1995). Furthermore, Tomasi et al's (2007) fMRI results demonstrated that compared to controls, cocaine users exhibited reduced levels of activation in the prefrontal regions relative to nonusers during the performance of a task loading on executive resources. Thus the cocaine-related deficit in source memory functioning may reflect a more general cocaine-related limitation in executive functioning. However, a degree of caution is warranted here since the present student sample will no doubt differ in many respects from the chronic cocaine users which featured in the above mentioned studies. It is also worthy of note that virtually all of the cocaine users in the present study also used ecstasy so the possibility that the two drugs interact in some way to produce the adverse effects observed here cannot be ruled out.

Both item and source memory involve the differential activation of information (e.g., in semantic memory) at encoding with source memory associated with greater levels of differentiation Anything that compromises attentional resources at the time of encoding (e.g., divided attention, brain damage) compromises source memory (Johnson et al. 1993). The integrity of attentional resources has been investigated in ecstasy/polydrug users. For example, Indlekofer et al. (2009) administered the Test for Attentional Performance (TAP) which examines several aspects of attentional processes. Following controls for age, sex, IQ, and the use of other illicit drugs and alcohol, aspects of ecstasy use significantly predicted omissions/errors on several of the TAP measures including alertness, managing stimulus incompatibility and vigilance (Indlekofer et al., 2009). It is possible therefore that the source memory deficits observed here may be a corollary of more general attentional problems.

However, only one of the ecstasy use measures was significantly associated with source memory while aspects of current cocaine use were more important in this regard. Thus the proposition that attentional resources may be responsible with the results obtained here is only partially supported.

A number of limitations need to be acknowledged in relation to the present study. In common with much of the existing literature, this study has relied on self-report data in relation to drug use. However, while objective measures would have been desirable, research suggests a high degree of concordance between self-report and objective measures of recent drug use from saliva (Yacoubian and Wish, 2006) and of longer term use from hair (Scholey et al. 2011; Vignali et al. 2012). Furthermore, concordance between self-reports and objective measures of drug use has been demonstrated for multiple illicit drugs (Vignali et al. 2012), cannabis and cocaine (Vignali et al. 2012; Zaldívar et al. 2009) and ecstasy (Scholey et al. 2011; Yacoubian and Wish, 2006).

A procedural limitation must also be acknowledged. As noted above, at the initial presentation words were either presented in upper or lower case. However, in the subsequent recognition test the words were all presented in upper case. In general terms, there is little doubt that reinstatement of contextual cues present during learning, facilitates memory performance at the time of recall/recognition. This has been demonstrated in a meta-analysis (Smith and Vela, 2001). Thus by implication, in the present study where the stimulus characteristics at initial learning and subsequent recognition were congruent (i.e., when the word was in upper case on both occasions) some facilitation might be expected. It is also possible that learning might be impaired when the characteristics were incongruent. Thus the group-related deficit we observed may stem from the fact that ecstasy/polydrug users were less able to benefit from the facilitatory effects of presentational congruence or more susceptible to the negative effects of incongruence. There is evidence to suggest that illicit

drug users may be adversely affected in the incongruent condition of the Stroop test (e.g., Halpern et al. 2004). However, there is reason to believe that such context dependent effects may be moderated by working memory (WM) capacity. Paradoxically although high WM persons benefited more than low WM when encoding and retrieval conditions matched, when they did not there was no effect of WM suggesting that high WM persons may be more disrupted by incongruity than low WM (Unsworth et al. 2011). In view of the fact that ecstasy/polydrug use has been associated with WM deficits (Murphy et al.2009) it may be that ecstasy/polydrug users in the present study may have been less affected by incongruence than the control group.

With regard to our findings, while we have noted the apparent role that cocaine has played in accounting for our results, we cannot exclude the possibility that other drugs may have played a part. Virtually all of the cocaine users in the present study also used ecstasy and cannabis. Therefore while the results obtained appear to relate to cocaine use we cannot exclude the possibility that cocaine might interact with other illicit drugs to produce its apparent effects in the present sample. It must also be acknowledged that despite the apparent dose related link between cocaine use and some aspects of source memory, the presence of cocaine use may be an indicator of other important lifestyle or premorbid characteristics which may be associated with worse cognitive outcomes in their own right as well as resulting in illicit drug use.

Lastly, it is noteworthy that there is a degree of missing data which is readily apparent comparing the sample sizes associated with the various measures in Table 2. Generally, participants were better able to report on the extent of their recent use and make categorical distinctions, e.g., whether or not they had ever used a particular drug, as opposed to confidently reporting longer term trends. In a few instances, responses were missing from the questionnaire possibly due to questions being overlooked. A degree of missing data is not

uncommon in studies of this kind (e.g., Bedi & Redman, 2008; Indlekofer et al. 2009). However, while we wished to avail ourselves of the largest possible sample for each of the comparisons in question, it should be borne in mind that some of the significant associations (or lack of them) reported in Table 2 relate to sub-sets of the data.

In conclusion, subject to the limitations noted above, to the authors' knowledge, the present study is the first to demonstrate source memory deficits among ecstasy/polydrug users. Furthermore these deficits appear to be associated with aspects of cocaine use. While they may diminish with increasing abstinence, in view of the role that source memory plays in everyday cognition, the presence of deficits among regular cocaine users is a cause for concern.

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Table 1 Demographic indicators by gender for ecstasy users and non-ecstasy users

	Ecstasy Users						Non ecstasy users						p (two tailed)		
	Male			Female			Male			Female			Drug	Gender	Drug* Gender
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n			
Age	22.59	2.52	37	21.60	2.10	25	21.19	1.82	27	20.48	2.27	48	.002	.033	.715
Ravens progressive matrices (maximum 60)	45.83	6.63	35	41.32	9.18	25	45.48	8.21	27	43.98	8.51	46	.427	.040	.302
Years of education	16.18	1.71	30	16.70	1.84	23	15.83	1.52	24	15.55	1.77	44	.022	.730	.220
Alcohol (units per week)	14.36	10.13	35	11.44	8.90	24	13.69	10.43	26	12.21	12.02	39	.979	.260	.713
Alcohol (length of use: weeks)	392.59	189.50	35	387.21	138.00	24	372.53	195.51	23	292.72	131.43	41	.062	.164	.224
Cigarettes per day	6.47	4.21	16	6.11	4.45	13	8.67	2.31	3	7.75	5.24	8	na	na	na

Table 2 Measures of drug use by sex for ecstasy users and non-ecstasy users

	Ecstasy Users						Non ecstasy users						p (two tailed)		
	Male			Female			Male			Female			Drug	Gender	Drug* Gender
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N			
Total Prior Consumption															
Cannabis (joints)	1772.34	3140.60	31	425.28	937.20	20	1812.77	3051.17	10	292.83	439.02	16	.937	.016	.882
Cocaine (lines)	424.11	759.80	24	1003.45	1558.94	16	4.16	-	1	104.39	100.56	2	na	na	na
Ecstasy (tablets)	629.81	1897.22	35	834.19	2705.61	22	-	-	-	-	-	--	-	.739	-
Long-Term Average Dose per Session															
Cannabis (joints)	3.00	1.92	31	1.51	0.81	20	1.82	1.31	10	1.79	0.81	16	.211	.034	.041
Cocaine (lines)	5.64	4.78	24	8.09	11.01	16	1.00	-	1	6.25	2.47	2	na	na	na
Ecstasy (tablets)	2.66	2.03	35	3.04	2.85	22	-	-	-	-	-	-	-	.559	-
Current Frequency of Use (times per week)															
Cannabis	3.87	11.08	32	1.00	1.91	21	1.37	2.57	13	0.46	1.02	18	.352	.248	.547
Cocaine	0.21	0.34	25	0.74	1.16	18	0.02	0.03	2	0.27	0.34	4	na	na	na
Ecstasy	0.21	0.41	37	0.23	0.44	25	-	-	-	-	-	-	-	.807	-
Amount Consumed in Previous 10 days															
Cannabis (joints)	4.94	15.25	34	2.25	8.48	22	1.60	3.07	15	0.89	2.00	18	.316	.468	.672
Cocaine (lines)	1.42	4.95	26	3.60	7.10	20	0.50	0.71	2	1.60	3.58	5	na	na	na
Ecstasy (tablets)	0.49	2.08	37	0.37	1.08	25	-	-	-	-	-	-	-	.793	-
Weeks Since Last Use															
Cannabis	26.05	46.99	33	43.03	76.66	22	80.85	92.24	15	55.87	98.07	17	.048	.813	.216
Cocaine	33.05	59.71	25	25.49	57.07	20	10.43	13.54	2	16.69	21.87	5	na	na	na
Ecstasy	50.87	69.70	37	54.74	82.68	25	-	-	-	-	-	-	-	.843	-

Table 3. Outcomes for source and item memory measures by sex for ecstasy users and non-ecstasy users

	Ecstasy Users						Non ecstasy users						p (two tailed)		
	Male			Female			Male			Female			Drug	Gender	Drug* Gender
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N			
Source Memory Component (% of Hits)															
Position	58.78	16.28	37	65.46	18.07	25	60.91	17.02	27	65.03	16.84	48	.776	.074	.670
List	61.23	10.16	37	56.26	17.89	25	59.53	9.63	27	64.50	16.34	48	.191	1.000	.048
Case	58.37	14.04	37	62.28	19.25	25	62.61	14.63	27	69.87	11.36	48	.022	.030	.512
Item Memory Outcomes															
Hits (number)	34.70	10.23	37	33.44	11.21	25	37.70	11.29	27	33.42	10.29	48	.430	.143	.423
False Positives (number)	13.32	12.09	37	9.96	10.25	25	9.89	9.74	27	7.21	9.88	48	.100	.108	.855
SDT Sensitivity (d prime)	1.08	0.70	35	1.18	0.87	23	1.40	0.82	26	1.43	0.78	44	.047	.635	.811
SDT Decision Criterion	0.41	0.49	35	0.58	0.48	23	0.48	0.40	26	0.69	0.43	44	.307	.020	.788

Table 4 The relationship between aspects of illicit drug use and source and item memory performance.

	Mean	SD	n	Zero-Order Correlation with:				
				Source Memory Component			SDT Measures	
				Position	List	Case	D Prime	Criterion
Alcohol								
Units per week	13.11	10.61	125	.005	-.090	-.026	.062	.016
Recent use (units, previous 10 days)	18.27	16.10	108	-.032	-.041	.095	.000	.000
Length of Use (weeks)	353.74	167.24	124	-.057	-.144	-.059	-.056	-.100
Illicit Drugs								
Total Prior Consumption								
Cannabis (joints)	1119.18	2384.65	78	-.093	-.099	-.007	-.053	.079
Cocaine (lines)	601.52	1123.45	44	-.008	-.110	.158	.022	-.095
Ecstasy (tablets)	696.75	2205.02	58	.018	-.176	.238(†)	.030	.183
Long-Term Average Dose per Session								
Cannabis (joints)	2.23	1.55	78	-.171	-.093	-.154	-.049	-.063
Cocaine (lines)	6.37	7.56	44	.000	-.050	.051	.010	.003
Ecstasy (tablets)	2.76	2.37	58	-.080	-.340**	.133	.071	.081
Current Frequency of Use (times per week)								
Cannabis	2.09	7.05	85	-.202†	.176	-.101	-.004	.066
Cocaine	0.40	0.77	50	.171	-..529***	-.347*	-.300*	.119
Ecstasy	0.22	0.42	63	-.125	-.105	.012	-.172	.076
Amount Consumed in Previous 10 days								
Cannabis (joints)	2.94	10.41	90	-.011	.007	.049	.017	-.006
Cocaine (lines)	2.19	5.64	54	.044	-.300*	.142	.133	.132
Ecstasy (tablets)	0.43	1.72	63	-.019	-.033	.075	-.004	.143
Weeks Since Last Use								
Cannabis	45.10	75.99	88	-.050	-.034	.114	.050	.060
Cocaine	27.25	54.09	53	.359**	.253†	.350*	.223	.216
Ecstasy	51.65	74.23	63	.242†	.155	.116	.151	-.032

*** p<.001; ** p<.01; * p<.05 † p<.10 two tailed

Figure 1:List Memory Judgements by User Group and Gender