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# THE EFFECTS OF RECREATIONAL DRUGS ON EMOTIONAL EPISODIC MEMORY

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# Abstract

Recently, there has been a resurgence in research exploring how certain psychoactive drugs might be used in the treatment of mental disorders associated with emotional episodic memory disturbances, such as posttraumatic stress disorder (PTSD). However, the effects of these drugs on particular stages of emotional episodic memory (i.e., encoding, consolidation, and retrieval) have not been properly isolated. The goal of this dissertation is to better understand the effects of these and other drugs of abuse on different stages of emotional and neutral memory, knowledge that is needed to maximize any benefits while minimizing the harms. In Chapter 1, I comprehensively review the scientific literature on the effects of the most commonly used and abused psychoactive drugs on the encoding, consolidation, and retrieval of emotional episodic memories. This review highlights the emotional selectivity of drug effects on memory, methodological considerations, and current gaps in the literature. This review also incorporates key findings from my own recent work, aimed at addressing some of these gaps, including three drug studies that are more fully described in Chapters 2, 3, and 4. In these subsequent chapters, I studied drugs that are commonly associated with PTSD because of their potential to impact emotional memories. In Chapter 2, I tested the effects of Δ9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, on the retrieval of emotional memories. It is known that THC attenuates the encoding of emotional memories more selectively than neutral memories, but its effects during the retrieval of emotional memories had never been tested. I show that THC robustly increases false memories with no evidence of memory suppression, which has implications for the use of cannabis in medicine. In Chapter 3, I provide the first test of ±3,4-methylenedioxymethamphetamine (MDMA) on the encoding and retrieval of emotional episodic memories. I demonstrate that MDMA has specific amnestic effects on emotional

memory encoding and to a lesser extent, emotional memory retrieval. Furthermore, I show that these effects only become apparent when using methods aimed at dissociating two fundamental episodic memory processes: recollection and familiarity. This finding is relevant to the use of MDMA-assisted psychotherapy in patients with PTSD. In Chapter 4, using the process dissociation procedures from Chapter 3, I reanalyzed a dataset in which the effects of alcohol were tested on the encoding and consolidation of emotional memories. This earlier study found that alcohol at encoding had emotionally selective amnestic effects, similar to THC and MDMA. In my reanalysis of this study, I found that alcohol impairs encoding and enhances consolidation of both recollection and familiarity. These findings are bolstered by my reanalysis of several previous studies that tested the effects of other $GABA_A$ positive allosteric modulators (PAMs) on encoding. Although the emotionally selective amnestic effects of alcohol and other $GABA_A$ PAMs may resemble those of THC and MDMA, the impact of these drugs on different episodic memory processes implicate distinct roles for each drug in medicine. Finally, I conclude with a discussion of the importance of dissociating component processes of episodic memory in pharmacology studies aiming to target aspects of memory that are dysfunctional in mental disorders. This discussion ends with clinical implications for PTSD, as well as addiction, and future directions that incorporate both behavioral manipulations and neuroimaging.

# Chapter 1:

# Recreational Drugs and Emotional Episodic Memory:

# Comprehensive Review of the

# Human Psychopharmacology Literature

Recreational drugs are known to modulate both emotional processing and episodic memory. These effects are of clinical importance because several mental disorders are related to both drug abuse and emotional memory disturbances. In this literature review, I comprehensively review human pharmacological studies investigating the impact of psychoactive drugs on emotional episodic memory encoding, consolidation, and retrieval, including studies from our own lab which have been some of the first to disentangle drug effects on these different stages of emotional memory in humans. The most consistent finding was that most drugs administered at encoding have a stronger impact on emotional compared to neutral memories: Memory-enhancing drugs disproportionately improve memories with emotional content, whereas memory-impairing drugs disproportionately impair memories with emotional content. Few studies have specifically examined the effects of drugs during the post-encoding consolidation phase, but a handful of emotional memory studies with post-encoding $GABA_A$ positive allosteric modulators (PAMs) have been conducted. In these studies, $GABA_A$ PAMs enhance memories for stimuli viewed before drug administration (i.e., retrograde facilitation). Moreover, the extent to which this effect is related to the emotional content of the stimuli depends on the delay between encoding and retrieval: Emotional memories are preferentially enhanced at short delays and neutral memories at longer delays. Finally, drugs administered specifically during the retrieval phase appear to increase false memories, especially for positive memories, across

several classes of drugs. We discuss potential neural mechanisms and highlight methodological considerations for each of these phase-dependent drug effects.

## Introduction

It is well known that psychoactive drugs can impact episodic memory and emotional processing in humans, yet only recently have researchers begun to explore the effects of drugs specifically on emotional memories. This avenue of research is timely, as some of these drugs are becoming more widely used and investigated for their clinical potential for psychiatric disorders (e.g., ±3,4-methylenedioxymethamphetamine, MDMA and cannabis). Moreover, several disorders such as depression, posttraumatic stress disorder (PTSD), and schizophrenia are associated with both abnormalities in emotional episodic memory (Brewin, 2011; Gotlib & Joormann, 2010; Herbener, 2008) and psychoactive drug use (Brown & Wolfe, 1994; Davis, Uezato, Newell, & Frazier, 2008; Volkow, 2009). It is possible that emotional memory disturbances can arise from drug use itself, but certain drugs may be able to effectively regulate emotional dysfunction in clinical, as well as healthy populations. Therefore, outlining the conditions that maximize any potential benefits while minimizing harms is crucial to public health.

Whereas many ideas surrounding drug-taking behavior focus on conditioned responses or emotion regulation from acute drug effects, less focus has been placed on the effects of drugs on different stages of episodic memory. Episodic memory is the ability to consciously remember past experiences (Tulving, 2002), and it is possible that drugs improve emotion regulation by affecting different phases or processes of episodic memory. Specifically, episodic memory can be separated into three different phases, encoding, consolidation, and retrieval, and how drugs differentially impact each of these stages of emotional memory processing could contribute to

emotion regulation. For example, drugs may alter the encoding of new emotional events by either dampening negative emotional information or enhancing positive emotional information so that what is remembered improves emotional states even when the drug is absent. Analogously, a much-needed vacation can provide positive memories or relief from negative events in one's life that can contribute to positive affect long after a vacation is over. Pleasurable "episodic drug memories" from periods of intoxication could also provide another reason for subsequent use, thereby highlighting a step in drug-taking behavior that precedes addiction (Müller, 2013). It is also well known that drugs are sometimes taken after a negative event takes place (i.e., during the consolidation window). As will be discussed, depending on the drug and timeframe, this can potentially worsen one's mental state by enhancing memory for negative memories. Finally, the way a drug affects memory retrieval, by suppressing or distorting emotional memories, may also have long-lasting consequences on memory traces that extend into sobriety.

Here, I comprehensively review the scientific literature on the effects of psychoactive drugs on emotional episodic memory encoding, consolidation, and retrieval in humans and the extent that these drugs specifically affect emotional compared to neutral memories. Emotion typically enhances processing during all stages of episodic memory, resulting in slower forgetting of emotional, compared to neutral, episodic memories (Bowen, Kark, & Kensinger, 2017; Mather, Clewett, Sakaki, & Harley, 2016; Yonelinas & Ritchey, 2015). Interestingly, it has now been shown across several studies that various drugs can bidirectionally modulate this emotional memory enhancement, especially when delays are implemented to isolate drug effects to one phase of memory.

I selected studies in which a psychoactive drug manipulation took place prior to the encoding, consolidation, or retrieval of an episodic memory task containing both emotional and neutral stimuli (unless otherwise stated). "Recreational" or "psychoactive" drugs were considered to be mood-altering substances that can be used nonmedically (e.g., for leisure or self-medication) and have a known abuse potential. I begin this discussion with the effects of several different classes of drugs on memory encoding, the phase of memory that most studies have targeted in an emotional memory task. Then I turn to how drugs can affect memory consolidation. This discussion is focused on $GABA_A$ positive allosteric modulators (PAMs), as these drugs have been the most commonly tested during the consolidation phase of an emotional memory task. Lastly, I discuss the few cases in which drug effects have been isolated to memory retrieval during an emotional memory task. Throughout this chapter, I will highlight commonalities and differences between the effects of different psychoactive drugs, methodological considerations, gaps in our current knowledge, and potential neural mechanisms. Included in this discussion is my own work that contributed to the conclusions and speculations drawn in this chapter. These studies will then be reported more extensively in Chapters 2, 3, and 4.

## Drug Effects on Emotional Memory Encoding

Most studies testing the effects of psychoactive drugs on emotional episodic memory in humans have examined the encoding phase. A common finding across several classes of drugs has been that whatever the main effect of a drug is on memory encoding, the effect will be greater for emotional information. That is, drugs that impair memory encoding and drugs that enhance memory encoding will impair and enhance, respectively, emotional memory to a greater extent than neutral memory. We discuss studies in which a psychoactive drug was administered

prior to the encoding phase of an emotional memory task and focus on studies that presented both neutral and emotional (negative or positive) stimuli to examine the specificity of drug effects on emotional episodic memory.

To identify psychoactive drug effects on emotional memory encoding I searched the literature for studies in which sedatives, cannabinoids, stimulants, dissociatives, entactogens, or psychedelics were administered prior to the encoding phase of an emotional memory task. The drugs identified and discussed here are $GABA_A$ PAMs (i.e., alcohol and benzodiazepines), Δ9-tetrahydrocannabinol (THC), dopaminergic-noradrenergic stimulants (i.e., dextroamphetamine, dextromethamphetamine, methylphenidate, MDMA), nicotine, and dissociatives (scopolamine and ketamine). In the following subsections, I focus on three aspects of drug effects on emotional memory encoding: selectivity for negative and positive memory, drug effects on emotional reactivity to encoded stimuli, and potential neural mechanisms.

**Selectivity for Negative and Positive Memories**

I begin my discussion with the $GABA_A$ PAMs benzodiazepines and alcohol, as these drugs have been the most studied class of psychoactive drugs in emotional memory research. Sedating drugs like these are widely abused in anxiety disorders and are strongly amnestic when delivered prior to encoding. Of relevance to their use in anxiety disorders, these amnestic effects are greater for emotional information.

To test the emotional specificity of $GABA_A$ PAMs on episodic memory, several studies have utilized a task originally developed by Cahill, Prins, Weber, and McGaugh (1994). This task presents a slide show with audio describing a story that contains an emotionally negative component that occurs between two relatively neutral parts of the story. Under drug-free conditions, recall and recognition of details from the emotional component of the story is better

than recall and recognition of the neutral components. However, when subjects received a benzodiazepine such as lorazepam or triazolam prior to encoding the story and then were tested two to seven days later (i.e., after drug effects have washed out), the mnemonic advantage for the emotional component of the story was abolished: That is, memory was equal for the emotional and neutral parts of the story (Brignell, Rosenthal, & Curran, 2007; Buchanan, Karafin, & Adolphs, 2003; Kamboj & Curran, 2006). Although there was also amnesia for neutral parts of the story, the amnestic effects were greater for the emotional component, suggesting that the drugs specifically attenuate emotional memory.

Although this story memory task has provided several key insights, it also has limitations. Because the negative emotional component of the story task always occurs between two neutral components, emotion may be confounded with serial order, making it difficult to distinguish whether drug effects are actually stronger for emotional material. A study utilizing a variant of the story task found that serial order did indeed interact with drug effects on emotional memory (Brown et al., 2010). Participants were either presented with an emotional or a neutral version of a story that included the same sequence of neutral pictures. What separated the emotional and neutral stories was the content of pictures that occurred immediately before and immediately after each neutral picture. These pictures that "sandwiched" the neutral pictures were emotionally negative in the emotional story and emotionally neutral in the neutral story, thereby creating an emotional context for the same neutral pictures used in both versions of the story. Alcohol or placebo was administered prior to viewing the story, and memory was tested for the neutral pictures. Consistent with the previously discussed $GABA_A$ PAM studies that used the story task, alcohol had its strongest amnestic effect on the encoding of the items presented in a negative emotional context. Nevertheless, this effect of alcohol was most apparent for items that

occurred at the beginning of the story, suggesting that selective drug effects for emotional episodic memories can interact with a primacy effect.

Another potential problem with the story tasks is that it does not include a positive emotional component, making it unclear if the drugs' effects are specific to negative valence or whether they apply to arousing material in general, including positive material. Negative emotional valence tends to prioritize memories to a greater degree than positive valence (cf. Bowen et al., 2017). Therefore, drugs may not necessarily impact negative and positive memories in the same way.

In contrast to the story task, lists of randomized negative, neutral, and positive pictures manipulates valence bidirectionally and controls for the effects of serial order. Our group and others have now tested the effects of various drugs at encoding on this kind of task. In one study, we administered alcohol prior to the encoding of these stimuli and tested memory two days later (Weafer, Gallo, & de Wit, 2016; see also Doss et al., submitted). Alcohol impaired both negative and positive picture recollections more than neutral picture recollections, suggesting that the selective emotional effects of $GABA_A$ PAMs on memory encoding apply to both emotionally negative and positive memories.

Importantly, not all studies have found emotionally selective effects with $GABA_A$ PAMs administered at encoding, potentially because of the timing between encoding and retrieval. For example, two studies with alcohol administered prior to encoding found equal memory impairments for neutral and emotional pictures (Knowles & Duka, 2004; Ray et al., 2012), and another study that administered the benzodiazepine diazepam prior to the encoding of emotionally negative and positive words found no memory impairment (Murphy, Downham, Cowen, & Harmer, 2008). In these studies, memory was tested soon after encoding while

participants were still intoxicated. Without a delay between encoding and retrieval, it is unclear if drug effects may have interacted with memory retrieval. Furthermore, it is known that benzodiazepines (Pagel & Parnes, 2001) and alcohol (Ebrahim, Shapiro, Williams, & Fenwick, 2013) suppress rapid eye movement (REM) sleep, a stage of sleep that appears to be especially important for emotional memory consolidation (Groch, Wilhelm, Diekelmann, & Born, 2013; Wagner, Gais, & Born, 2001). It may be that emotionally specific encoding effects only appear after a sufficient delay between encoding and retrieval, thereby allowing lingering drug effects to interact with consolidation processes during sleep. Analogously, the enhancements in emotional compared to neutral memory are also more apparent after longer delays between encoding and retrieval (Yonelinas & Ritchey, 2015).

Like $GABA_A$ PAMs, cannabis and its main psychoactive constituent, THC, impair memory encoding (for review, see Curran et al., 2016) and reduce REM sleep (Babson, Sottile, & Morabito, 2017), and similarly, THC appears to have greater effects on the encoding of emotional, compared to neutral, stimuli. Our group has found that the amnestic effects of THC on encoding were larger for negative and positive pictures compared to neutral pictures (Ballard, Gallo, & de Wit, 2013). Similar to those studies that demonstrated emotionally selective amnestic effects with $GABA_A$ PAMs, this study also included a delay (two days) between encoding and retrieval. Together, these findings suggest that the interval between encoding and retrieval may influence how drugs differentially affect emotional and neutral memories.

Interestingly, it appears that certain drugs can selectively enhance emotional compared to neutral memory, and some evidence suggests that these effects are also related to subsequent sleep quality. In two studies, our group has found that the dopaminergic-noradrenergic stimulants dextroamphetamine and dextromethamphetamine during encoding enhanced memory

preferentially for negative and positive pictures compared to neutral pictures (Ballard et al., 2013; Ballard, Weafer, Gallo, & de Wit, 2015). Both of these studies included a two-day delay between encoding and retrieval, but the longer half-life of dextromethamphetamine resulted in several participants reporting sleep disturbances the night after their encoding session. These participants did not show emotionally selective memory enhancements but instead were found to have impaired memory for negative pictures. Because stimulants impair REM sleep (Rechtschaffen & Maron, 1964) like $GABA_A$ PAMs and THC, inadequate REM sleep may preclude selective encoding enhancements of emotional memory and potentially even disrupt the consolidation of negative memories.

Not all studies have found that stimulant drugs preferentially affect emotional content. Brignell et al. (2007) administered the dopaminergic-noradrenergic stimulant methylphenidate during encoding of the story task and tested memory seven days later. Methylphenidate did not affect emotional memory, though it did enhance memory for the neutral components of the story task that occurred prior to and after the emotional component. As previously discussed, serial order may interact with drug effects in this kind of task. For example, methylphenidate might have enhanced primacy and recency effects, thereby occluding selective emotional memory enhancements.

Whereas dextroamphetamine and dextromethamphetamine selectively enhanced emotional memory, I recently demonstrated that the related amphetamine drug, MDMA, produced opposite results (described in detail in Chapter 3). This study examined the effects of MDMA on the encoding of negative, neutral, and positive pictures (Doss, Weafer, Gallo, & de Wit, 2018). Two days after encoding, memory was tested in a sober state, and it was found that MDMA impaired negative and positive recollections but not neutral recollections. One reason

for this discrepancy between MDMA and typical stimulants (i.e., dextroamphetamine and dextromethamphetamine) may be attributed to the racemic mixture of MDMA that was used. Like typical stimulants, the *S*-enantiomer of MDMA is a monoamine reuptake inhibitor and releasing agent but with stronger effects on synaptic serotonin (Pitts et al., 2018). In contrast, the *R*-enantiomer has some affinity for the serotonin 2A receptor, which underlies psychedelic effects of drugs like lysergic acid diethylamide and psilocybin. Modulation of the serotonin 2A receptor appears to underlie MDMA's amnestic effect on encoding (van Wel et al., 2011), though it is unclear if serotonin 2A stimulation is also sufficient to produce the selective emotional memory impairments. Regardless of the precise mechanism, it is interesting that MDMA's effects on norepinephrine and dopamine, common to memory-enhancing stimulants, do not simply "cancel out" its amnestic effects.

Nicotine, a cholinergic agonist with stimulant properties, is another drug that has been tested during the encoding phase of an emotional memory task. In one study, nicotine enhanced memory encoding equally for both neutral and emotional words (Froeliger, Gilbert, & McClernon, 2009), though this study tested memory soon after encoding. As discussed, including a delay between encoding and retrieval might be an important boundary condition for emotionally selective drug effects on encoding to become apparent. Interestingly, scopolamine, a cholinergic antagonist occasionally used recreationally for its dissociative effects, has been shown to have emotionally selective amnestic effects during the encoding of the story task when memory is tested seven days later (Kamboj & Curran, 2006). By inference, enhancing cholinergic activity with nicotine may reveal larger enhancements in emotional memory encoding if a longer delay were implemented between encoding and retrieval.

One last psychoactive drug that has been tested on emotional memory encoding is the anesthetic dissociative ketamine. In terms of its emotional specificity, it may be somewhat of an outlier. In a functional magnetic resonance imaging (fMRI) study, Becker et al. (2017) administered ketamine prior to the encoding of negative, neutral, and positive pictures in the scanner and tested memory five days after encoding. Although there was an overall memory impairment, there was evidence for greater specificity for positive but not negative memory. Interestingly, their neuroimaging findings may speak to why there was not also a greater impairment for negative compared to neutral memories. Amygdalar activation was increased by ketamine selectively during the encoding of negative pictures. Given the importance of the amygdala for emotional episodic memory encoding (for review, see Yonelinas & Ritchey, 2015), these findings suggest that the increased amygdalar activation during encoding may have protected negative memories from preferential amnestic effects that have been observed with other psychoactive drugs. Whereas the emotionally selective effects of other drugs on memory encoding could be attributed to modulations of arousal because both negative and positive memories were affected (but see section on emotional reactivity below), ketamine's selectivity for positive memories would suggest that valence too might play a role in some of these emotionally selective effects (cf. Bowen et al., 2017).

**Drug Effects on Emotional Reactivity to Encoded Stimuli**

Because several emotional memory studies implemented ratings of emotional reactivity (i.e., subjective valence and arousal ratings) during the encoding phase, I turn to how drug effects on these ratings may play a role in subsequent effects on emotional episodic memory. Greater negativity and arousal ratings have been linked to better memory (e.g., Grühn & Scheibe, 2008; Marchewka et al., 2016). Therefore, it might be predicted that if a given drug reduces or

increases subjective reactivity to emotional stimuli that this should be associated with reductions or increases, respectively, in memory encoding.

Our group has found that there does not appear to be a one-to-one mapping between drugs effects on the subjective evaluation of emotional stimuli and emotional memory. For example, in Weafer et al. (2016) and Doss et al. (2018), alcohol and MDMA were not found to affect valence or arousal ratings, yet both drugs at encoding impaired emotional memory more selectively than neutral memory. Consistent with these findings, a recent study directly stimulated the human amygdala during encoding at an intensity that did not evoke subjective emotional responses, yet delayed memory was still found to be enhanced (Inman et al., 2018). These findings suggest that the emotional selectivity of drug effects on memory encoding cannot be solely explained by drug-induced changes in emotional reactivity.

Some drugs do significantly impact subjective valence and arousal ratings, but these effects are not necessarily indicative of changes in emotional memory. Ballard et al. (2013) found that THC impaired memory for negative and positive pictures, and at a lower dose (7.5 mg), it increased arousal and negativity ratings, mostly for neutral pictures, perhaps suggesting that these effects may have preserved memory for neutral items. However, Ballard et al. also found dextroamphetamine to increase ratings of positivity and arousal across all pictures, but memory was only significantly improved for negative and positive pictures. Finally, in Becker et al. (2017), ketamine paradoxically increased ratings of arousal for positive pictures yet decreased memory more selectively for these same items.

Although one reason for these discrepancies between drug effects on emotional processing and memory encoding may be that some drugs have greater selectivity for the brain's episodic memory network, another reason may be that drug effects tend to linger post-encoding.

That is, there may be subsequent effects on consolidation that may interact with those during encoding. As we have discussed, this may especially be the case when sleep is impacted by lingering drug effects. Future work with post-encoding sleep recordings and measures of memory at different time lags will help in resolving the relationship between drug effects on emotional processing, memory encoding, and memory consolidation. Furthermore, as discussed later, drug effects on consolidation can be qualitatively quite different from those on encoding.

**Neural Underpinnings**

A potential common pathway to selective drug effects on emotional memory encoding may involve the amygdala. Various drugs appear to modulate the amygdala's response to emotional stimuli, and one possibility may be that amnestic drugs impair the amygdala's ability to bind item and emotion information (Yonelinas & Ritchey, 2015). $GABA_A$ PAMs (Del-Ben et al., 2010; Gilman et al., 2008; Paulus et al., 2005), THC (Phan et al., 2008), and MDMA (Bedi, Phan, Angstadt, & de Wit, 2009) have all been found to reduce amygdalar activation to emotional stimuli (specifically, negative emotional faces), findings that may support their larger impact on the encoding emotional compared to neutral material. In contrast, ketamine, which had stronger amnestic effects for positive memories only, was shown to enhance amygdalar activation during the encoding of negative stimuli, thereby explaining potentially why negative items were less affected (Becker et al., 2017). To our knowledge, this is the only simultaneous pharmaco-fMRI study that has measured emotional episodic memory. Finally, dextroamphetamine, which enhanced emotional memory encoding, increases amygdala activation to emotional stimuli (Hariri et al., 2002). Together, these findings suggest that drug effects on the amygdala may underlie the selectivity of psychoactive on emotional memory encoding.

## Drug Effects on Emotional Memory Consolidation

In the previous section, we discussed how implementing a delay between encoding and retrieval can increase the likelihood of revealing emotionally selective drugs effects on memory encoding, and this also controls for concurrent drug effects on memory retrieval. However, longer delays between encoding and retrieval also allow more time for lingering drug effects to impact the post-encoding consolidation phase. Although it is difficult to completely decouple the effects of drugs administered at encoding from those on subsequent consolidation, it is possible to isolate drug effects on consolidation by administering drugs immediately post-encoding. In the case of some drugs, pre- vs. post-encoding administration can produce drastically different effects on emotional memory. Specifically, in contrast to their impairing effects at encoding, $GABA_A$ PAMs can paradoxically enhance memory when administered immediately post-encoding (a phenomenon known as "retrograde facilitation").

Because the vast majority of emotional memory studies with post-encoding drug manipulations have used $GABA_A$ PAMs, we begin our discussion in this section with retrograde facilitation studies that presented both neutral and emotional material during encoding. As is revealed by comparison across these studies, the delay between encoding and retrieval may determine whether emotional memory is selectively enhanced. We then discuss potential neural mechanisms for these effects, proposing that memory reactivations during sleep may especially be involved. Finally, we conclude with a short discussion of studies that have utilized post-encoding manipulations with other drugs, in most cases resulting in no significant effects.

### Retrograde Facilitation via $GABA_A$ PAMs

Whereas pre-encoding $GABA_A$ PAMs impair memory, especially for emotional stimuli, post-encoding $GABA_A$ PAMs enhance memory, sometimes preferentially for emotional

memory. One explanation for this phenomenon is that $GABA_A$ PAMs prevent new long-term potentiation (LTP) in the hippocampus while preserving pre-drug LTP, resulting in reductions in retroactive interference (for discussion, see Wixted, 2004). Another possibility is that post-encoding $GABA_A$ PAMs directly facilitate consolidation processes. Although reductions in retroactive interference likely explain some of these effects (e.g., Mueller, Lisman, & Spear, 1983; Tyson & Schirmuly, 1994), evidence indicates that this account does not completely explain the selective facilitation of emotional memories. In one study (Knowles & Duka, 2004) participants encoded negative, neutral, and positive pictures followed by the administration of alcohol or placebo and a memory test. They found that retroactive enhancements from alcohol were somewhat exaggerated for the recall of emotional pictures (collapsed across negative and positive pictures) compared to neutral pictures. However, because they tested memory soon after the administration of alcohol, it is unclear if these effects of alcohol can be attributed to consolidation or retrieval. Some evidence suggesting that alcohol accelerated consolidation comes from the fact that larger differences in memory for emotional compared to neutral stimuli typically occur with longer delays between encoding and retrieval (Bowen et al., 2017; Yonelinas & Ritchey, 2015). Furthermore, as discussed later, psychoactive drugs do not typically enhance memory when administered at retrieval.

Recent work has shown that certain consolidation processes during sleep are actually enhanced by the $GABA_A$ PAM zolpidem, and these enhancements are associated with improvements in emotional memory (Kaestner, Wixted, & Mednick, 2013). In this study, participants encoded negative, neutral, and positive pictures followed by the administration of a placebo or zolpidem. After the drug manipulation, participants took a nap that included one REM cycle. Memory was then tested several hours later, potentially when drug effects on memory

retrieval were minimized, though unlikely to be completely gone. Post-encoding zolpidem led to enhancements in memory specifically for negative pictures, as well as for highly arousing pictures, thereby replicating the emotional specificity of retrograde facilitation via alcohol when memory was tested soon after encoding (Knowles & Duka, 2004). Furthermore, this facilitation was associated with increased sleep spindle density, suggesting that in addition to processes during REM sleep (Groch et al., 2013; Wagner, Gais, & Born, 2001), processes during non-REM sleep are also important for emotional memory consolidation. It is unclear, however, if these effects of zolpidem apply to other $GABA_A$ PAMs, as hypnotics are thought to impact sleep differently than other $GABA_A$, including less suppression of REM sleep (Besset et al., 1995).

In contrast to work with shorter delays between encoding and retrieval, when longer delays are implemented, the selectivity of retrograde facilitation for emotional compared to neutral memory appears to diminish, disappear, or even reverse. In a study by Bruce and Pihl (1997), a one-day delay was included between the encoding and retrieval of negative, neutral, and positive verbal statements. Post-encoding alcohol similarly enhanced the recall of neutral and emotional statements, though selective emotional enhancements were found on a subsequent recognition memory test. A study with a similar design but without neutral stimuli found retrograde facilitation of positive but not negative statements, which was mediated by whether alcohol had a stimulant-like effect (Bruce, Shestowsky, Mayerovitch, & Pihl, 1999b). However, this individual difference finding was not replicated when an incidental encoding procedure was used (Bruce, Pihl, Mayerovitch, & Shestowsky, 1999a). Finally, when our group tested memory for negative, neutral, and positive pictures two days after encoding, post-encoding alcohol retroactively enhanced memory only for neutral pictures. As is reported in more detail in Chapter 4, I reanalyzed these data and found a trend for positive memory to be retroactively enhanced as

well (Doss et al., submitted). Together, these findings suggest that retrograde facilitation of emotional information by alcohol may be fleeting over longer delays, though perhaps less so for positive material.

**Neural Underpinnings of Retrograde Facilitation**

Although differences in procedures may underlie the discrepancies in the findings above, there are several possible neural events that may explain why negative memories are less likely to benefit from retrograde facilitation over longer delays. The most parsimonious explanation may be that arousing memories, especially negative ones, are more robustly encoded (e.g., greater item-emotion binding) such that these memories would be less likely to benefit from reductions in retroactive interference. Another possibility is that given the importance of REM sleep for emotional memory (Groch et al., 2013; Wagner, Gais, & Born, 2001), reductions in REM sleep from $GABA_A$ PAMs may have destabilized these memories. Finally, all $GABA_A$ PAMs appear to prolong non-REM sleep (e.g., Ebrahim et al., 2013; Mednick et al., 2013), a period during which memories strengthen via hippocampal reactivations (Rasch & Born, 2008; Walker, 2009). However, negative memories require coordinated reactivations between the hippocampus and amygdala (Girardeau, Inema, & Buzsáki, 2017), and $GABA_A$ PAMs have been found to dampen amygdalar activity during the processing of negative emotional information (Del-Ben et al., 2010; Gilman et al., 2008; Paulus et al., 2005). Dampened amygdala activity may reduce the likelihood that negative memories reactivate during the first night of sleep. Reactivations during subsequent nights of sleep may then become less and less likely, thereby explaining the preferred enhancements for neutral memories over longer time lags. Future work will be needed to resolve the time-dependent nature of enhancing emotional memories via retrograde facilitation.

**Other Post-Encoding Drug Manipulations**

Few studies exist testing the effects of other recreation drugs during the consolidation window of emotional memories or neutral memories, but surprisingly, other post-encoding amnestic drugs do not seem to enhance memory. For example, post-encoding smoked marijuana was not found to affect the recall of neutral verbal stimuli in a study that found retroactive enhancements with post-encoding alcohol (Parker et al., 1980). Post-encoding sodium oxybate, an amnestic $GABA_B$ agonist, also had no effect on emotional or neutral memories in a study that found zolpidem to enhance memory especially for negative memories (Kaestner et al., 2013). Like zolpidem, sodium oxybate was found to prolong non-REM sleep, but in spite of this longer period for sleep spindles to occur, sodium oxybate reduced sleep spindles. Together, these findings suggest that amnestic drugs other than $GABA_A$ PAMs may too reduce retroactive interference, but their alterations to sleep-based consolidation processes might counteract any benefit to memory.

The finding that participants who experienced stimulating effects of alcohol predicted whether positive memories would be retroactively enhanced (Bruce et al., 1999b) might suggest that a post-encoding stimulant manipulation should enhance positive memory. Such an enhancement from post-encoding dextroamphetamine has been found for appetitive memories in rodents (Simon & Setlow, 2006). However, work from our group failed to find any effect of post-encoding dextromethamphetamine on emotional or neutral episodic memories in humans (Ballard et al., 2015). One reason for this null effect might have been that memory performance was near ceiling in those participants whose sleep was not disrupted by dextromethamphetamine. Another possibility is that memory consolidation was enhanced, but dextromethamphetamine simultaneously enhanced encoding that occurred after the encoding phase of the experiment,

thereby increasing retroactive interference and counteracting any benefit. These studies of drug effects on consolidation, as well as those on encoding, highlight how drugs may impact multiple processes over the course of emotional memory processing.

## Drug Effects on Emotional Memory Retrieval

To date, there have only been a few studies isolating drug effects during emotional episodic memory retrieval in humans, all by our group. Like our encoding studies, participants encoded negative, neutral, and positive pictures, and we tested memory 48 hours later so that memories had some time to consolidate unperturbed by a drug manipulation. In three studies, we have administered dextroamphetamine, MDMA, and THC just prior to the memory test (the latter two studies are reported in detail in Chapters 2 and 3). As descried in the first subsection below, the first consistent finding we discuss from these studies is that drugs at retrieval increase false alarms. In the second subsection, we discuss that this propensity for memory distortion to be stronger for positive memories. Although this latter finding is not usually very robust, we speculate on why it might exist and potential mechanisms that may underlie it. In the final subsection, we conclude with a discussion of how drug effects on the ventral striatum may produce these illusory memories.

### Driving False Memories

In contrast to drug effects at encoding, selective effects on emotional memory retrieval have been less consistent, though one consistency across drugs appears to be increases in false memories. Dextroamphetamine during retrieval was found to increase recall intrusions of verbal and picture stimuli and false recognition of words across emotional and neutral items (Ballard, Gallo, & de Wit, 2014). Similarly, we found trends for MDMA during retrieval to increase false alarms, including high confidence false alarms, on a picture recollection test (Doss et al., 2018).

This propensity to increase false memories is not limited to stimulants at retrieval, as evidence suggests that cannabis and THC may also distort memory retrieval. Recently, I found that THC during retrieval robustly increased high confidence false recollections across emotional valences and several measures (Doss, Weafer, Gallo, & de Wit, in review). Similar findings have been observed in several studies administering smoked marijuana (Hart et al., 2010; Ilan, Smith, & Gevins, 2004; Miller, Cornett, & McFarland, 1978; Miller, McFarland, Cornett, & Brightwell, 1977), though in these studies the drug had been administered prior to encoding with an immediate memory test. Therefore, it was unclear whether these memory errors were due to drug effects on encoding or retrieval. Given that false alarms were not elevated when we administered THC prior to encoding and memory was tested sober (Ballard et al., 2013) nor were false alarms increased by amphetamine (Ballard et al., 2013) or MDMA (Doss et al., 2018) at encoding, it appears that various psychoactive drugs during retrieval increase memory errors.

Although one study testing alcohol specifically during free recall one week after sober encoding did not find greater memory intrusions (Birnbaum, Parker, Hartley, & Noble, 1978), in Doss et al. (submitted), I searched for all studies that administered $GABA_A$ PAMs prior to encoding and used the remember/know procedure (Tulving, 1985) at retrieval. Across the eight studies that reported false alarms, no delay was included between encoding and retrieval, and therefore, drug effects remained at retrieval. There was a trend for overall false alarms and false alarms accompanied by "remembering" (i.e., the recollection of details and associations) to be increased. In contrast, when a two-day delay was implemented between encoding and retrieval, our group did not find that alcohol at encoding or consolidation increased false alarms (Weafer et al., 2016). These findings suggest that $GABA_A$ PAMs at retrieval may also be capable of

distorting memory. Consistent with this idea, the barbiturate and $GABA_A$ PAM amytal has been found to contribute to false memory formation when used in psychotherapy (Piper, 1993).

**Selectivity for Distorting Positive Memories**

Another potential commonality between drug effects on memory retrieval is that these memory distortions appear to be strongest for positive memories. In Ballard et al. (2014), dextroamphetamine facilitated the recall of true and false details only for words and pictures that had been subjectively rated as positive. Similarly, we found that the MDMA-driven increases in false alarms were most apparent for positive material (Doss et al., 2018). Finally, Doss et al. (in review) found that THC increased multiple measures of false alarms, including high confidence false recollections, most robustly for positive material.

Although the statistical support for this specificity of drugs to distort positive memories has been rather weak, some evidence suggests that positive memories are more distortable than negative memories. Several studies have shown that memories for autobiographical events that were perceived as positive were less accurately but more confidently reported than memory for those same events when they were perceived as negative (Bohn & Bernstein, 2007; Kensinger & Schacter, 2006; Levine & Bluck, 2004). Similarly, exposure to positive reviews but not negative reviews for a fictitious product can create false memories of having experienced the fictitious product (Montgomery & Rajagopal, 2018). Carhart-Harris et al. (2014) found that MDMA during autobiographical memory retrieval increased subjective vividness for positive memories but not negative ones (see also Carhart-Harris et al., 2012 for a similar finding with the psychedelic psilocybin). Because our study found that MDMA during retrieval, if anything, suppressed memory for emotionally positive stimuli, it is possible that the increases in subjective memory vividness are not necessarily accurate. This tendency toward forming favorable

memories, regardless of their veracity, could be viewed as an enhanced optimism bias (Sharot, 2011), which may contribute to drug use.

### Neural Underpinnings

All psychoactive drugs modulate the ventral striatum (Yager, Garcia, Wunsch, & Ferguson, 2015), and although speculative, it is possible that modulation of this area by drugs during memory retrieval attempts may be a common pathway to illusory recollections. The ventral striatum is thought to be involved with memory retrieval (King et al., 2017; Scimeca & Badre, 2012), including the retrieval of positive autobiographical memories (Speer, Bhanji, & Delgado, 2014) and false memory retrieval (Abe et al., 2008). Furthermore, Bedi et al. (2009) found ventral striatal activation to positive but not negative faces while participants were on MDMA, and Gilman et al. (2010) found that neutral but not negative faces activated the ventral striatum while participants were on alcohol. Thus, the heightened ventral striatal activity from processing positive (or less negative) stimuli during drug intoxication may contribute to the tendency to more selectively creating positive false memories.

## Summary

This review surveyed the literature exploring how various psychoactive drugs exhibit selective effects on emotional episodic memories depending on the phase of memory processing. Drugs that impair encoding are more amnestic for emotional memories, and drugs that enhance encoding more selectively enhance emotional memories. Retrograde facilitation of emotional memories with $GABA_A$ PAMs appears to be time-dependent such that longer delays between encoding and retrieval will reveal less emotional memory enhancements. Finally, a few different drugs appear to increase false memories when administered during retrieval with this effect

perhaps being greater for positive memories. In Table 1, we summarize these findings, as well as gaps in our current knowledge.

| | Encoding | | | Consolidation | | | Retrieval | | |
|---|---|---|---|---|---|---|---|---|---|
| | Negative | Neutral | Positive | Negative | Neutral | Positive | Negative | Neutral | Positive |
| $GABA_A$ PAMs | <Hits | <Hits | <Hits | >Hits* | >Hits* | >Hits* | ? | ? | ? |
| Sodium Oxybate | ? | ? | ? | - | - | - | ? | ? | ? |
| THC | **<Hits** | <Hits | **<Hits** | ? | - | ? | >FAs | >FAs | **>FAs** |
| DA/NE Stimulants | **>Hits** | >Hits | **>Hits** | - | - | - | >FAs | >FAs | **>FAs** |
| MDMA | **<Hits** | <Hits | **<Hits** | ? | ? | ? | >FAs | >FAs | **>FAs** |
| Scopolamine | **<Hits** | <Hits | ? | ? | ? | ? | ? | ? | ? |
| Ketamine | **<Hits** | <Hits | **<Hits** | ? | ? | ? | ? | ? | ? |



**Table 1.** Summary of drug effects on emotional episodic memory. Studies were considered that tested emotional and neutral memory with delays between encoding and retrieval so that drug effects can be properly isolated to different phases of memory. Bold font indicates greater specificity for emotional compared to neutral material. * = mixed results, ? = yet to be tested, - = null result.

# Chapter 2:

# Δ9-Tetrahydrocannabinol at Retrieval Drives False Recollection of Neutral and Emotional Memories

As discussed in Chapter 1, most research testing the effects of psychoactive drugs on emotional episodic memory comes from experiments in which a drug was administered prior to encoding with only a few cases in which a drug manipulation was isolated to retrieval. Although several studies have administered cannabis or THC prior to encoding and tested memory while participants were still intoxicated (Hart et al., 2010; Ilan, Smith, & Gevins, 2004; Miller, Cornett, & McFarland, 1978; Miller, McFarland, Cornett, & Brightwell, 1977), memory impairments and distortions were presumed to be due to drug effects on encoding. Recently, when the effects of THC were isolated to encoding (and potentially consolidation), our group has found memory impairments were larger for emotional compared to neutral memory with no concurrent increases in measures of memory distortion (Ballard et al., 2012, 2013). In this chapter, I report an experiment aiming to address gaps in our current knowledge regarding how THC impacts emotional memory retrieval.

One hypothesis from this study was that similar to encoding, THC would impair the retrieval of memories, especially emotional ones. This emotional memory suppression may be one reason why patients with PTSD use cannabis at high rates. Another hypothesis comes from work that found cannabis to cause memory distortions when administered prior to encoding with memory tested immediately after encoding (Hart et al., 2010; Ilan et al., 2004; Miller et al., 1977, 1978). These findings were perhaps due to drug effects persisting through memory retrieval, but the experimental design of these studies did not allow for drug effects to be differentiated

between encoding and retrieval. This memory distortion hypothesis would be consistent with the effects of other psychoactive drugs isolated to memory retrieval (Ballard et al., 2014; Doss et al., 2018).

To anticipate the experiment's results, I only found evidence for the latter hypothesis using two independent tasks and multiple measures. THC during retrieval did not reduce the number of correct responses to studied items. Instead, it robustly increased false recollection on both an emotional memory and false memory task. This effect was found for both neutral and emotional items. These findings show that in addition to the known impairments during encoding, THC also has adverse effects during memory retrieval, distorting memory for both neutral and emotional events. These findings are important in light of the spreading acceptance of cannabis.

## Background

Despite the rising acceptance of medical and recreational cannabis, surprisingly little is known about the effects of THC – the primary psychoactive ingredient of cannabis – on basic mechanisms of episodic memory in humans. Although it is well established that THC impairs episodic memory when it is administered during the encoding phase (for review, see Curran et al., 2016), it is less clear how the drug affects episodic memory during retrieval. In many past studies the encoding and retrieval phases of memory were not distinguishable: Cannabis or THC was administered before encoding and then participants were tested soon afterward so that retrieval also occurred under the drug's influence (e.g., Ilan, Smith, & Gevins, 2004; Miller, McFarland, Cornett, & Brightwell, 1977). This timing of the drug administration makes it difficult to determine if memory impairments were related to encoding, retrieval, or both. To isolate encoding effects, we previously administered THC during encoding and tested memory

48 hours later in a drug-free state (Ballard, Gallo, & de Wit, 2012, 2013). This work confirmed that THC impairs memory encoding. In contrast, a recent study examining the effect of THC only during retrieval found a null effect of THC on the recall of neutral verbal stimuli (Ranganathan et al., 2017). Taken together, this work suggests that THC has a larger impact on encoding, though many questions about the potential impact of THC at retrieval remain.

One open question is whether the potential impact of THC during episodic memory retrieval depends on the emotional content of the material. Prior research indicates that THC specifically attenuates the encoding of emotional compared to neutral episodic memories (Ballard et al., 2013), and in general, THC has been found to impair emotional processing (Ballard, Bedi, & de Wit, 2012; Hindocha et al., 2015) and reduce amygdala activations to emotional stimuli (Phan et al., 2008). If THC during retrieval similarly impairs memory and emotional processes, one might expect THC to disproportionately impair the retrieval of emotional compared to neutral recollections. Indeed, individuals with posttraumatic stress disorder (PTSD), a disorder characterized by aberrant negative recollections (Rubin et al., 2008), are known to use cannabis at high rates (Grant, Pedersen, & Neighbors, 2016; Kevorkian et al., 2015), and anecdotally, they report that the drug helps suppress the impact of retrieving emotionally negative memories. Thus, it is possible that THC has effects during retrieval that are greater for emotional memories.

In addition to reducing memories for studied events, THC at retrieval may increase false recollections of nonstudied events (i.e., high confidence memory errors). THC is known to disrupt processing in prefrontal cortex (Bossong et al., 2012a, 2012b), an area important for retrieval monitoring processes used to avoid false memories (Gallo, 2006). This prefrontal disruption would predict that THC at retrieval might increase false recollection. In addition, THC

and other recreational drugs impact the ventral striatum (Yager, Garcia, Wunsch, & Ferguson, 2015), a region involved in episodic memory retrieval (Scimeca & Badre, 2012), including emotional and false memory effects (Speer, Bhanji, & Delgado, 2014; Abe et al., 2008). Although the exact role of ventral striatum in episodic memory is still unclear, recent studies indicate that other drugs impacting this region can increase memory distortion. Administering dextroamphetamine during retrieval increases recognition and recall errors, especially for positive memories (Ballard, Gallo, & de Wit, 2014), and similar effects have been reported for ±3,4-methylenedioxymethamphetamine (MDMA; Doss, Weafer, Gallo, & de Wit, 2018). A similar effect of THC would be problematic if the drug is used to treat PTSD.

Based on these considerations, we hypothesized that THC during retrieval would reduce memory for studied events and increase false memory of nonstudied events. To test these hypotheses, we administered THC during the retrieval phase of two memory tests. One task was an emotional memory test sensitive to drug effects on emotional and false recollection (Doss et al., 2018). The other task was the Deese-Roediger-McDermott (DRM) illusion, a task involving episodic memory for emotionally neutral words that has been used to study false memory and drug effects (for review, see Gallo, 2010), including a previous study with a THC at encoding manipulation (Ballard et al., 2012).

## Methods

### Participants

Twenty-four healthy young adults (18-29 years, 12 males) with some experience using cannabis (4-100 lifetime occasions) were recruited for the study, but one male participant was excluded for not following instructions, leaving 23 participants. Screening included a physical examination, an electrocardiogram, and a semi-structured interview by a clinical psychologist.

Exclusion criteria included any current Axis I DSM-IV disorder, including substance dependence, current use of >5 cigarettes per day, history of psychosis or mania, less than a high school education, lack of English fluency, a body mass index outside 19-33 $kg/m^2$, high blood pressure (>140/90), abnormal electrocardiogram, daily use of any medication other than birth control, pregnancy, or lactating. Women not taking hormonal contraceptives were tested during their follicular phase because hormonal fluctuations can influence responses to drugs (White, Justice, & de Wit, 2002). Demographic and drug use information was obtained during screening (Table 2).

| | Mean (SEM) |
|---|---|
| *Age (years)* | 22.74 (.73) |
| *Education (years)* | 15.30 (.37) |
| *BMI* | 24.62 (.72) |
| *Caffeine (cups/day)* | 1.37 (.28) |
| *Nicotine (cigarettes/day in the five users)* | .19 (.15) |
| *Alcohol (drinks/week)* | 6.01 (1.32) |
| *Cannabis (uses/month)* | .78 (.26) |
| *Lifetime uses of Cannabis* | 27.26 (5.25) |
| *Last use of cannabis before Placebo session (days)* | 308.59 (189.59) |
| *Last use of cannabis before THC session (days)* | 306.02 (189.71) |

**Table 2.** Demographic data of participants in Chapter 2.

Qualifying participants attended an orientation session to sign a consent form and practice memory tasks (i.e., participants knew their memories would be tested). To minimize expectancy, participants were told that they could receive a stimulant, sedative, cannabinoid, or placebo. They were instructed to consume their normal amounts of caffeine and nicotine before sessions but abstain from using alcohol, prescription drugs (except contraceptives), and over-the-counter drugs for 24 hours before the encoding sessions (i.e., the first and fourth sessions; see Design below), cannabis for 1 week before the encoding sessions, and other illicit drugs for 48 hours before the encoding sessions (due to faster clearance). They were also told to remain abstinent from drugs and alcohol throughout the study, and they were advised that each session would begin with a drug test. Positive tests led to rescheduling or dismissal. Participants were advised to get their normal amounts of sleep and not to eat for two hours before retrieval sessions. Following completion of the study, participants were fully debriefed and monetarily compensated. The study took place at the University of Chicago Medical Center and was approved by the Institutional Review Board.

**Drug**

Fifteen mg of THC (Marinol®; Solvay Pharmaceuticals) was placed in opaque size 00 capsules with dextrose filler. Placebo capsules contained only dextrose. This dose of THC is within the range shown to affect memory in previous studies (Ballard et al., 2012, 2013).

**Design**

This study used a double blind, within-subjects, counterbalanced design in which participants were tested during memory retrieval with THC or placebo. Each experimental arm consisted of an encoding session followed 48 hours later by a retrieval session. Experimental arms were separated by at least five days, and drug order was counterbalanced across

participants. During the encoding session of each experimental arm, participants viewed emotional stimuli and DRM stimuli. During the second session, memory for the emotional stimuli and DRM stimuli was assessed. Participants completed additional tasks on this session and during an additional brief visit, but these will be reported elsewhere.

**Stimuli**

Stimuli for the emotional memory task consisted of 240 images from the International Affective Picture Set (IAPS; Lang et al., 2008) and the Nencki Affective Picture System (NAPS; Marchewka, Zurawski, Jednoróg, & Grabowska, 2014) and 3-5 word labels (e.g., "skinhead posing with Nazi flag", "boy leaning against wall", "man on snowy mountain peak") describing these images. Pictures were selected with an effort to balance semantic overlap between valence conditions, as this has been shown to be a factor in prior work (Gallo, Foster, & Johnson, 2009). The images included emotionally negative, neutral, and positive pictures (80 each), and these were divided into four comparable sets (A-D) for counterbalancing across participants' studied and nonstudied items (targets and lures, respectively; see Procedure below). Specifically, sets A and B were always administered during the first experimental arm and sets C and D were always administered during the second experimental arm. For half the participants (balanced for drug order and sex), Sets A and C were targets and sets B and D were lures, and for the other half of participants sets B and D were targets and sets A and C were lures. These sets had similar normed valences and arousals.

DRM stimuli consisted of 30 lists of 10 semantically related words that converge on a critical lure that is only presented at retrieval (e.g., "bed, rest, awake…" for critical lure "sleep"). These were the same lists used in (Ballard et al., 2012). For counterbalancing, these lists were split into two sets (A and B) of 15 lists for each experimental arm. Half the participants

(balanced for drug order and sex) received set A during the first experimental arm and set B during the second experimental arm, and the other half received the other order. In each set, 10 of the lists always served as targets and critical lures, and the other 5 lists were used to draw unrelated lures.

**Procedure**

At the beginning of all laboratory visits, participants completed compliance measures including breath alcohol level (Alco-sensor III, Intoximeters, St. Louis, MO), a urine drug test (ToxCup, Branan Medical Co. Irvine, CA), a pregnancy test (females only; Aimstrip, Craig Medical, Vista, CA), and baseline cardiovascular and mood measures. During the first session of each experimental arm, participants encoded the emotional stimuli consisting of 120 randomized labels, half of which were followed by their corresponding picture (each on screen for 2000 ms). For each label, participants rated how arousing each label was while the label was on the screen (five-point scale). When a picture was presented, participants again rated its arousal while it was on the screen. Between each trial was a random intertrial interval (ITI) between 1000-5000 ms. This task lasted approximately 15 minutes.

Next, participants encoded 10 DRM lists of 10 words each. The order of lists was randomized, but words within a list were presented in descending order relative to their semantic relatedness to the critical lure. Each word was presented for 2500 ms, and participants were required to make a pleasantness rating (“pleasant” or “unpleasant”) while the word was still on the screen. Between each word was a 500 ms ITI, and between each list was a screen that displayed “next list” for 3000 ms. This task lasted approximately 10 minutes, and afterward, participants left the lab.

Forty-eight hours later, participants returned to the lab and after compliance measures, consumed a capsule containing THC or placebo. Cardiovascular and mood measures were taken every 30 minutes for the next 120 minutes while the drug was absorbed (Wachtel et al., 2002). During this time, participants were provided with magazines and music in furnished rooms. They were not allowed to eat, sleep, or work, and they had no access to cell phones or Internet.

After 120 minutes, participants were tested with cued recollection and picture recognition tests for the emotional stimuli and a word recognition test for the DRM stimuli (all self-paced). For the cued recollection test, participants first viewed each label on screen for 1000 ms before they could make a response to allow sufficient time for a recollection response (Yonelinas, 2002). Then participants were asked whether they had seen the corresponding picture of each label (yes/no). Afterward, they rated their confidence on a five-point scale and were encouraged to use the entire scale. After the cued recollection test, participants viewed each picture (again on screen for 1000 ms before a response could be made) and indicated if they had previously seen it (yes/no). When a picture was recognized, they were asked if they "remember" the picture or they simply "know" it was presented (Yonelinas, 2002). They were instructed to give a "remember" response when they could recollect associated details from the event, such as thoughts during its presentation, and a "know" response when they simply knew that a picture had been presented without recollecting specific details. Together, these memory tests lasted approximately 30 minutes.

After the emotional memory tests, participants were tested on the DRM stimuli. This test was composed of 30 trials: 10 targets (first position in DRM list), 10 critical lures, and 10 unrelated lures (first position and critical lure from the 5 nonstudied DRM lists). On each trial, a word was presented (on screen for 1000 ms before a response could be made), and participants

indicated whether they had seen it (yes/no). In the instructions, participants were warned that there would be nonstudied related words, and they should only press "yes" if they had actually seen the word in one of the lists. Prior work with the DRM task has used this warning procedure to isolate false recognition errors that are driven by a strong sense of false recollection, as opposed to familiarity-based guessing (Gallo, 2006). This test lasted approximately 5 minutes.

After the DRM test, participants performed two other tasks and then were allowed to relax with magazines and music. Participants were allowed to leave 210 min post-capsule ingestion if physiological and subjective measures had returned to baseline.

**Dependent Measures**

Physiological and mood measures were obtained to monitor expected drug effects (Table 3). Heart rate and blood pressure were measured using a portable blood pressure monitor (A&D Medical/Life Source, San Jose, CA). Mood measures included the Addiction Research Centre Inventory (ARCI; Martin, Sloan, Sapira, & Jasinski, 1971), the Visual Analog Scales (VAS; Folstein & Luria, 1973), the Drug Effects Questionnaire (DEQ; Morean et al., 2013), and an End of Session Questionnaire (ESQ). The Addiction Research Centre Inventory measures drug-specific effects on a 56-item true-false questionnaire. For this study, we report the composite score of 12 questions that make up the marijuana scale (Chait, Fischman, & Schuster, 1985). The Visual Analog Scales is composed of thirteen adjectives used to assess individual dimensions of subjective mood – anxious, stimulated, sedated, elated, insightful, sociable, confident, lonely, playful, dizzy, loving, friendly, and restless, rated on a sliding scale from 'not at all' to 'extremely.' The Drug Effects Questionnaire is composed of five questions concerning current drug effects – how much participants feel a drug effect, like the effect, dislike the effect, feel high, and want more of the drug, rated on a sliding scale from 'not at all/neutral' to 'very much.'

Participants were instructed to select ‘not at all/neutral’ if they had not yet received a capsule. The End of Session Questionnaire asks participants what class of drugs they thought they received at the end of each session.

| | Placebo | THC |
|---|---|---|
| *Physiology* | | |
| Heart Rate | -7.00 (1.91) | **.23 (2.47)** |
| Systolic BP | -3.45 (2.07) | **1.05 (1.62)** |
| Diastolic BP | -1.91 (1.71) | -.68 (1.81) |
| | | |
| *ARCI* | | |
| Marijuana scale | .41 (.31) | **4.50 (.72)** |
| | | |
| *VAS* | | |
| Anxious | -5.00 (6.14) | 1.82 (2.94) |
| Stimulated | -7.23 (5.46) | 11.59 (6.53) |
| Sedated | -1.77 (7.21) | -5.00 (5.31) |
| Elated | -12.23 (5.47) | 5.59 (5.71) |
| Insightful | -10.41 (6.02) | 8.45 (5.95) |
| Sociable | -10.68 (4.39) | **11.23 (4.34)** |
| Confident | -8.18 (5.16) | 5.5 (5.00) |
| Lonely | -1.23 (4.65) | 1.59 (2.23) |
| Playful | -10.14 (4.47) | **13.05 (5.57)** |
| Dizzy | -4.00 (4.66) | 2.00 (4.30) |
| Loving | -2.64 (6.18) | 2.64 (4.18) |
| Friendly | -8.91 (5.69) | **13.45 (5.44)** |
| Restless | -5.77 (8.19) | 4.73 (5.52) |
| | | |
| *DEQ* | | |
| Feel drug effect | 4.64 (1.67) | **44.82 (6.50)** |
| Like drug effect | 12.23 (4.74) | **33.45 (6.67)** |
| Dislike drug effect | 8.41 (3.88) | **24.68 (5.71)** |
| Feel high | 3.72 (2.26) | **41.00 (6.37)** |
| Want more drug | 8.68 (4.08) | **22.86 (5.14)** |
| | | |
| *ESQ (percent who guessed receiving)* | | |

**Table 3.** Physiological and subjective measures in Chapter 2. Mean (SEM) values are changes from pre-capsule to immediately before retrieval (120 minutes). Bold values indicate significant differences ($p < .05$) between drug and Placebo conditions (*t* test). ARCI = Addiction Research Centre Inventory, VAS = Visual Analog Scales, DEQ = Drug Effects Questionnaire, ESQ = End of Study Questionnaire.

| | | |
|---|---|---|
| stimulant | 4.35 | 8.70 |
| sedative | 26.09 | 17.39 |
| cannabinoid | 0 | 73.91 |
| placebo | 69.57 | 0 |

**Table 3** continued.

For the cued recollection test, hit and false alarm rates were calculated for each valence and drug condition in each participant. False alarms were subtracted from hits to compute memory accuracy. Finally, high confidence hits, false alarms, and accuracy were calculated by only including responses with the top two levels of confidence. High confidence false alarms are a hallmark of false recollection (Gallo, 2006).

For the picture recognition test, hits, false alarms, accuracy, recollection hits (*p*("remember"|old)), recollection false alarms (*p*("remember"|lure)), and recollection accuracy were calculated for each valence and drug condition. Because a "know" response is the probability of familiarity in the absence of recollection, independence remember/know (IRK) familiarity estimates were computed to avoid underestimation (Yonelinas, 2002). An IRK familiarity hit estimate was therefore calculated as *p*("know"|target)/(1 - *p*("remember"|target)), false alarm estimate as *p*("know"|lure)/(1 - *p*("remember"|lure)), and accuracy estimate was the difference between these two values. In order to avoid dividing by 0, floor and ceiling hits and false alarms were replaced by .5/*N* and 1 - .5/*N*, respectively, where *N* is the maximum number of hits and false alarms that could be made (Macmillan & Creelman, 1991).

For the DRM recognition test, hit rates to targets and false alarm rates to critical and unrelated lures were calculated. To correct for baseline responding, adjusted hit and false alarm rates can be calculated by subtracting false alarm rates to unrelated lures (Gallo, 2006).

**Statistical Analysis**

The effects of THC on cardiovascular and subjective measures (changes from baseline) were compared to placebo using two-tailed *t* tests. Cued recollection hits, false alarms, accuracy, and high confidence measures were also submitted to 2 × 3 ANOVAs. Picture recognition hits, false alarms, accuracy, recollection hits, recollection false alarms, recollection accuracy,

familiarity hit estimates, familiarity false alarm estimates, and familiarity accuracy estimates were submitted to 2 × 3 ANOVAs (SI). For the DRM task, two-tailed *t* tests were conducted to compare placebo and drug condition hits, adjusted hits, and adjusted false alarms. False alarms were submitted to a 2 (drug) × 2 (lure type) ANOVA. When sphericity was violated, a Greenhouse-Geisser correction was applied to the degrees of freedom.

# Results

## Cued Recollection

Full cued recollection data can be found in Table 4. Cued recollection hit rates were directly related to valence (hits: $F(2, 44) = 27.371$, $p < .001$, $\eta_p^2 = .554$; high confidence hits: $F(2, 44) = 29.709$, $p < .001$, $\eta_p^2 = .575$). As expected, negative stimuli were remembered better than neutral and positive stimuli (Figures 1a and 2a). Relative to placebo, THC did not affect hits ($F(1, 22) = 2.025$, $p = .169$) or high confidence hits ($F(1, 22) = .062$, $p > .250$) nor did it modulate the effect of valence (hits: $F(2, 44) = .958$, $p > .250$; high confidence hits: $F(1.582, 34.798) = .437$, $p > .250$), inconsistent with the hypothesis that THC at retrieval would reduce memory for emotional events.

| | *Placebo* | | | *THC* | | |
|---|---|---|---|---|---|---|
| | Negative | Neutral | Positive | Negative | Neutral | Positive |
| *Encoding* | | | | | | |
| Label | 3.03 (.14) | 1.84 (.09) | 2.35 (.12) | 3.17 (.14) | 1.95 (.10) | 2.50 (.11) |
| Picture | 1.80 (.08) | 1.05 (.05) | 1.49 (.06) | 1.83 (.06) | 1.05 (.06) | 1.43 (.07) |
| *Cued Recollection* | | | | | | |
| Hits | .75 (.03) | .56 (.05) | .62 (.05) | .78 (.03) | .64 (.03) | .63 (.04) |
| FAs | .11 (.02) | .12 (.02) | .12 (.02) | .22 (.03) | .26 (.04) | .28 (.05) |
| Accuracy | .65 (.04) | .44 (.05) | .50 (.04) | .56 (.04) | .38 (.05) | .35 (.04) |
| Hi Conf Hits | .61 (.04) | .41 (.04) | .43 (.05) | .62 (.04) | .44 (.04) | .42 (.04) |
| Hi Conf FAs | .03 (.01) | .03 (.01) | .02 (.01) | .09 (.03) | .09 (.03) | .10 (.03) |
| Hi Conf Acc | .58 (.04) | .38 (.04) | .41 (.05) | .53 (.04) | .35 (.04) | .31 (.04) |
| *Picture Recognition* | | | | | | |
| Hits | .89 (.02) | .86 (.04) | .84 (.04) | .92 (.02) | .89 (.03) | .91 (.02) |
| FAs | .03 (.01) | .07 (.01) | .06 (.01) | .14 (.03) | .19 (.03) | .18 (.04) |
| Accuracy | .87 (.02) | .80 (.04) | .78 (.04) | .78 (.04) | .70 (.03) | .73 (.04) |
| R Hits | .67 (.04) | .51 (.04) | .50 (.05) | .67 (.05) | .53 (.05) | .54 (.05) |
| R FAs | .03 (.00) | .03 (.00) | .03 (.00) | .04 (.01) | .06 (.01) | .05 (.01) |
| R Acc | .65 (.04) | .48 (.04) | .48 (.05) | .64 (.06) | .47 (.05) | .49 (.05) |
| IRK F Hits | .68 (.05) | .76 (.06) | .70 (.05) | .74 (.06) | .76 (.04) | .79 (.04) |
| IRK F FAs | .04 (.01) | .08 (.01) | .07 (.01) | .14 (.03) | .16 (.03) | .17 (.03) |
| IRK F Acc | .64 (.05) | .68 (.05) | .63 (.05) | .60 (.06) | .60 (.04) | .63 (.04) |

**Table 4.** Encoding, cued recollection, and picture recognition data in Chapter 2. Values are means with SEM in parentheses. Cued R = cued recollection, Pic Rec = picture recognition, FA = false alarm, Hi Conf = high confidence, Acc = accuracy, R = recollection, IRK = independence remember/know, F = familiarity.

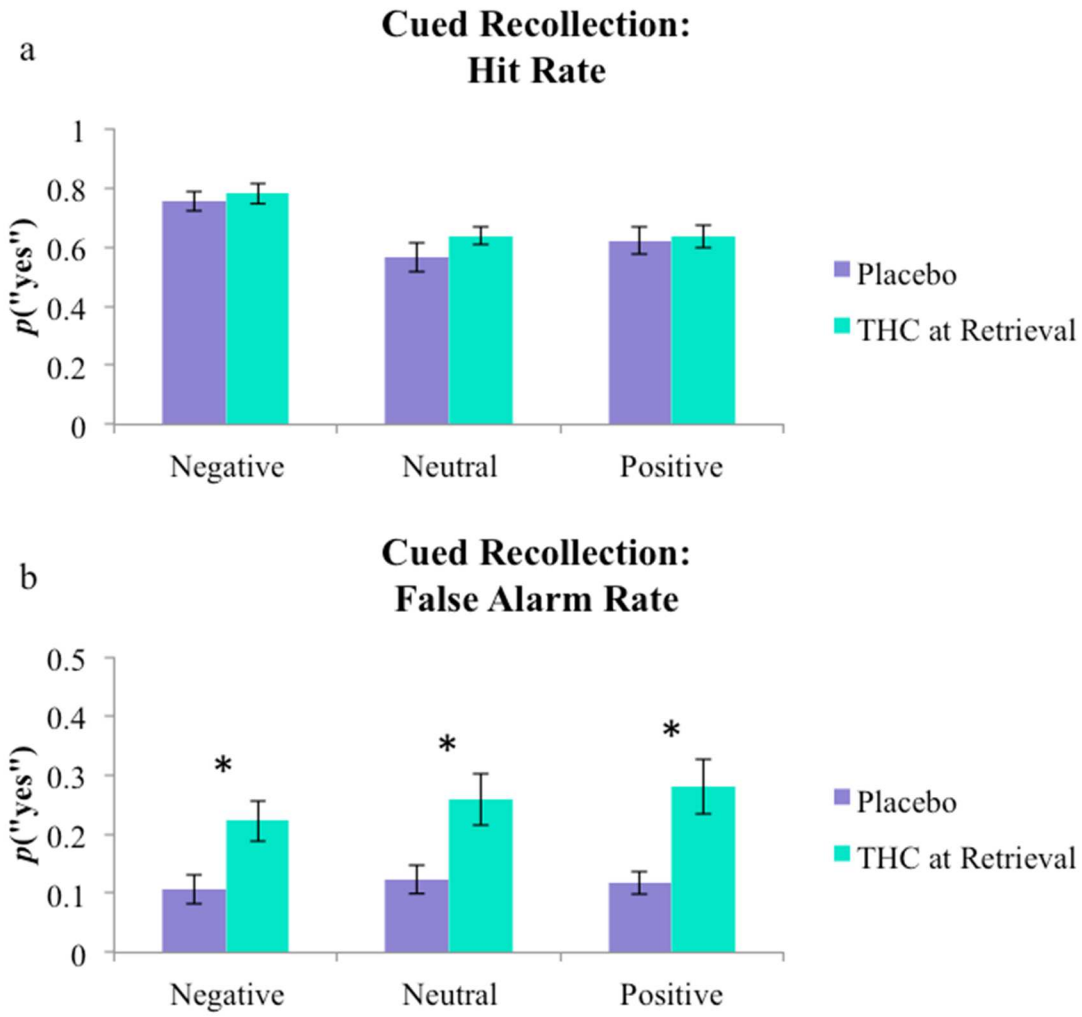


**Figure 1.** Mean **a.** hit and **b.** false alarm rates on the cued recollection task (all confidence responses included) in Chapter 2. Error bars are SEM. Asterisks indicate $p < .05$.

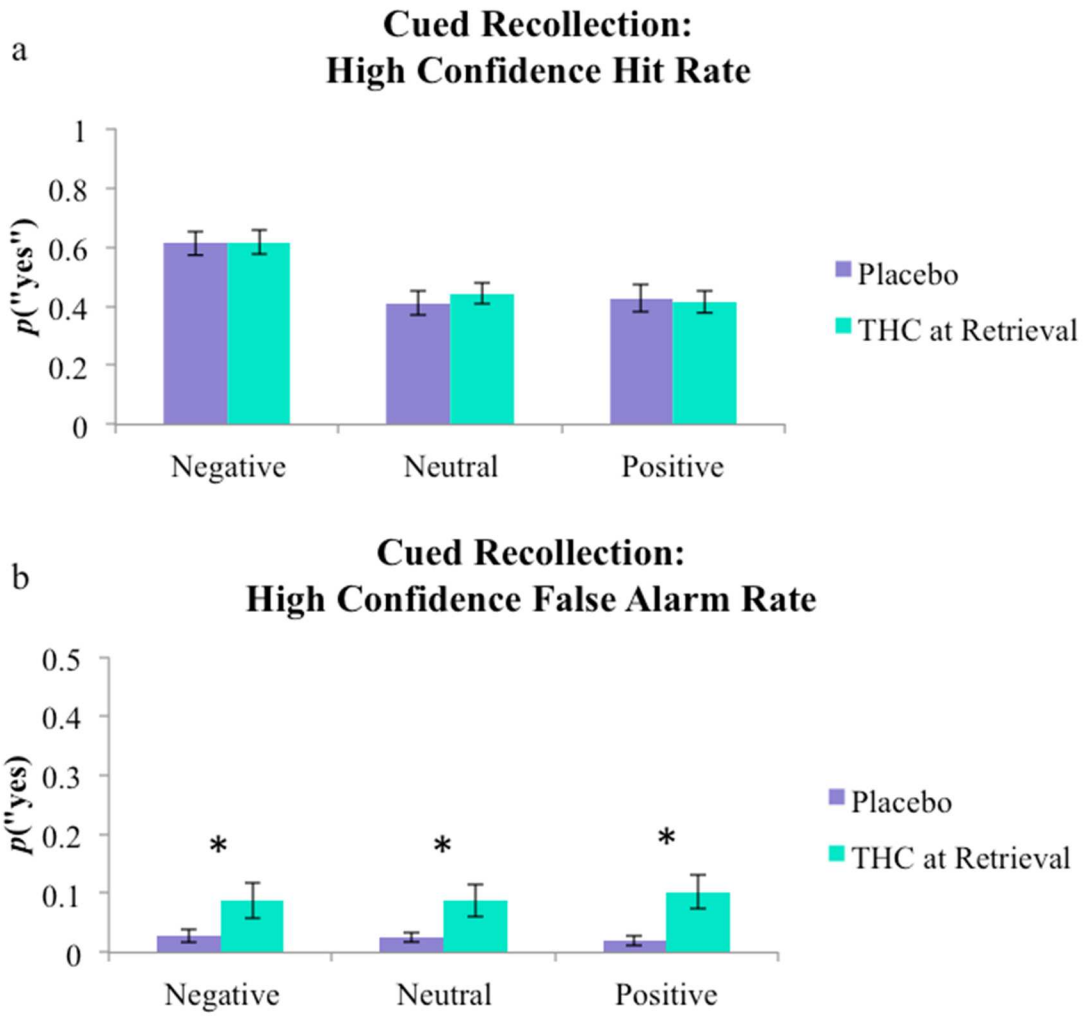


**Figure 2.** Mean high confidence **a.** hit and **b.** false alarm rates on the cued recollection task in Chapter 2. Error bars are SEM. Asterisks indicate $p < .05$.

In contrast to hits, THC significantly increased false alarms ($F(1, 22) = 10.269$, $p = .004$, $\eta_p^2 = .318$) and high confidence false alarms ($F(1, 22) = 5.655$, $p = .027$, $\eta_p^2 = .204$) relative to placebo (Figure 1b and 2b). Valence did not modulate false alarms ($F(1.586, 34.899) = 1.800$, $p = .186$), high confidence false alarms ($F(2, 44) = .114$, $p > .250$), or the effect of THC (false alarms: $F(2, 44) = 1.003$, $p > .250$; high confidence false alarms: $F(2, 44) = .922$, $p > .250$). Because THC increased false alarms, this led to a marginal reduction in accuracy ($F(1, 22) = 3.959$, $p = .059$, $\eta_p^2 = .153$) but not high confidence accuracy ($F(1, 22) = 1.814$, $p = .192$). There was also a main effect of valence on accuracy ($F(2, 44) = 29.753$, $p < .001$, $\eta_p^2 = .575$) and high confidence accuracy ($F(2, 44) = 26.471$, $p < .001$, $\eta_p^2 = .546$), as memory was more accurate for negative compared to neutral or positive items, and the drug by valence interaction was not significant (accuracy: $F(2,44) = 1.642$, $p = .205$; high confidence accuracy: $F(2,44) = .919$, $p > .250$).

Although THC during retrieval significantly increased false alarms, this effect was not related to the emotional content of the stimuli. Nevertheless, we examined this relationship more closely because previous studies have found trends for other drugs to have greater effects on memory errors for positive material (Ballard et al., 2014; Doss et al., 2018). Indeed, the effect of THC on false alarms in the present study appeared to be largest for positive items (negative: $t(22) = 2.853$, $p = .017$, $d = .538$; neutral: $t(22) = 2.637$, $p = .015$, $d = .550$; positive: $t(22) = 3.569$, $p = .002$, $d = .744$). This numerical trend was also found in high confidence false alarms (negative: $t(22) = 1.783$, $p = .088$, $d = .372$; neutral: $t(22) = 2.193$, $p = .039$, $d = .458$; positive: $t(22) = 2.702$, $p = .013$, $d = .563$).

**Picture Recognition**

Picture recognition data can be found in Table 4. THC during retrieval increased raw hit rates ($F(1, 22) = 6.320$, $p = .020$, $\eta_p^2 = .223$), but produced an even greater effect on false alarm rates ($F(1, 22) = 21.357$, $p < .001$, $\eta_p^2 = .493$), resulting in reduced accuracy ($F(1, 22) = 5.970$, $p = .023$, $\eta_p^2 = .213$). There was also a trending effect of valence on hits ($F(2, 44) = 2.966$, $p = .062$, $\eta_p^2 = .119$) and a significant effect of valence on false alarms ($F(2, 44) = 4.406$, $p = .018$, $\eta_p^2 = .167$). Because hits were greatest and false alarms were reduced for negative pictures, there was a main effect of valence on accuracy ($F(2, 44) = 10.402$, $p < .001$, $\eta_p^2 = .321$). The drug by emotion interactions for hits ($F(2, 44) = 1.080$, $p > .250$), false alarms ($F(2,44) = .010$, $p > .250$), and accuracy were not significant ($F(2, 44) = .494$, $p > .250$).

The recollection responses were largely consistent with the cued recollection data. THC during retrieval did not modulate recollection hit rates ($F(1, 22) = .266$, $p < .250$) or recollection accuracy ($F(1, 22) = .000$, $p > .250$), but recollection was related to valence on both (hit rates: $F(2, 44) = 29.728$, $p < .001$, $\eta_p^2 = .575$; accuracy: $F(2, 44) = 33.506$, $p < .001$, $\eta_p^2 = .603$), due to greater recollection for negative material. Additionally, the drug's effects were not related to valence for either recollection hit rates ($F(2, 44) = .425$, $p > .250$) or recollection accuracy ($F(2, 44) = .223$, $p > .250$). Because no recollection-based false alarms were reported in the placebo condition and recollection false alarms were at floor in the THC condition, main effects of valence and the interaction are difficult to interpret (and in fact, were statistically equal and nonsignificant; $F(2, 44) = 1.775$, $p = .181$). Nevertheless, consistent with the cued recollection data, THC significantly increased recollection-based false alarms ($F(1, 22) = 6.361$, $p = .019$, $\eta_p^2 = .224$).

Turning to the IRK familiarity estimates, THC did not alter IRK familiarity hit estimates ($F(1, 22) = 1.687$, $p = .207$) or IRK familiarity accuracy ($F(1, 22) = 1.233$, $p > .250$), but it did increase IRK familiarity false alarm estimates ($F(1, 22) = 18.985$, $p < .001$, $\eta_p^2 = .463$). In contrast to the recollection responses, valence did not modulate IRK familiarity estimates (hit estimates: $F(1.325, 29.141) = .859$, $p > .250$; false alarm estimates: $F(2, 44) = 2.189$, $p = .124$; accuracy estimates: $F(1.345, 29.585) = .192$, $p > .250$), though there appeared to be a trend for IRK familiarity false alarms to be greater for positive material. The drug by valence interactions were not significant (hit estimates: $F(2, 44) = .797$, $p > .250$; false alarm estimates: $F(2, 44) = .273$, $p > .250$, accuracy estimates: $F(2, 44) = .519$, $p > .250$). The effect of THC on increasing IRK familiarity false alarms was observed for all emotional categories (negative: $t(22) = 3.333$, $p = .003$, $d = .695$; neutral: $t(22) = 3.635$, $p = .001$, $d = .758$; positive: $t(22) = 3.515$, $p = .002$, $d = .733$).

**DRM Recognition**

Full DRM recognition data can be found in Table 5. THC during retrieval did not affect hit rates ($t(22) = 0.000$, $p > .250$), but as with the emotional memory tests, it significantly elevated false alarms (Figure 3; $F(1, 22) = 12.388$, $p < .002$, $\eta_p^2 = .360$). This effect did not differ for critical lures or unrelated lures ($F(1, 22) = .862$, $p > .250$). Because unrelated lure false alarms were elevated, adjusted hit rates were attenuated by THC ($t(22) = 3.393$, $p = .003$, $d = .708$), but the concurrent elevation in false alarms to critical and unrelated lures led to no significant difference in drug conditions for adjusted false alarms ($t(22) = .928$, $p > .250$).

| | Placebo | THC |
|---|---|---|
| Hits | .76 (.04) | .76 (.04) |
| Critical FAs | .50 (.04) | .60 (.04) |
| Unrelated FAs | .21 (.03) | .37 (.05) |
| Adjusted Hits | .55 (.04) | .39 (.05) |
| Adjusted FAs | .29 (.04) | .23 (.04) |

**Table 5.** DRM recognition data in Chapter 2. Values are means with SEM in parentheses. FA = false alarm.

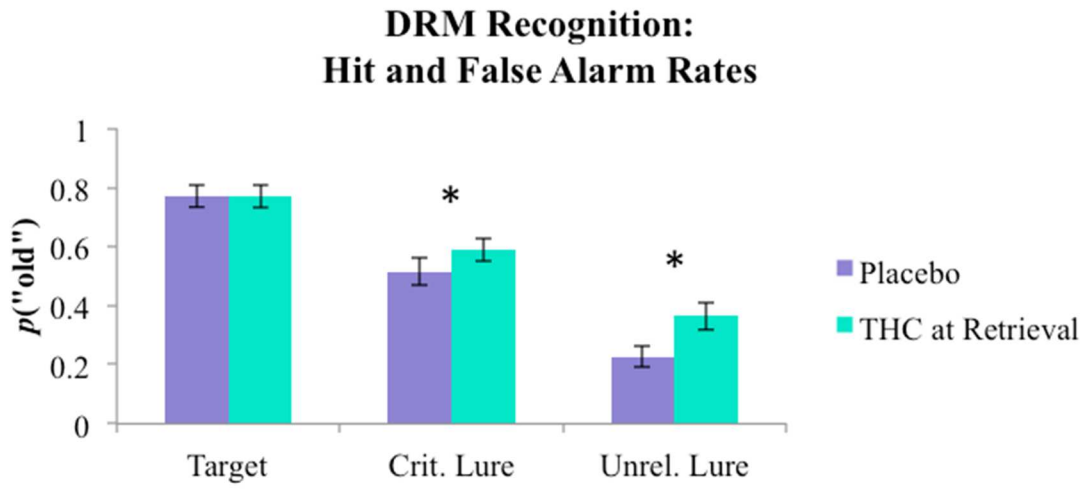


**Figure 3.** Mean hit and false alarm rates on the DRM task in Chapter 2. Error bars are SEM. Asterisks indicate $p < .05$.

## Discussion

This experiment is the first to find that selectively administering THC during episodic memory retrieval increases false recollection. Evidence for this effect was found across all emotional valences in the emotional memory task and also for neutral words in the DRM task. These findings are consistent with studies using emotionally neutral verbal stimuli showing that THC increases false recognition (Hart et al., 2010; Ilan et al., 2004) and recall intrusions (Miller et al., 1977; Miller, Cornett, & McFarland, 1978). However, in those studies participants were intoxicated during both encoding and retrieval. Although a recent study failed to find an effect of THC during the recall of neutral verbal stimuli (Ranganathan et al., 2017), that study did not include measures of memory intrusions.

Considered with our prior studies using these tasks, the current results show that THC has different effects during encoding and retrieval, highlighting the importance of drug studies that separate the two phases. Specifically, selectively administering THC during encoding primarily reduced memory for studied pictures and words in the emotional memory task and the DRM task, respectively (Ballard et al., 2012, 2013). By contrast, the current study indicates that selectively administering THC during retrieval primarily increased false recollection of nonstudied pictures and words in these tasks.

It is possible that these THC effects on memory retrieval could be driven by a change in response bias, or a willingness to give an affirmative memory response at test in the absence of memory retrieval. However, we believe that THC during retrieval increased false recollections. The emotional memory task we used encouraged participants to recollect the pictures, and drug effects were found in both high confidence errors (cued recollection test) and subjective recollection judgments (recognition test). Moreover, for the DRM task, we warned participants

during retrieval to avoid falsely recognizing semantically related words. Thus, in addition to increasing familiarity-based errors, we found that THC increased false recollection errors using two different memory tasks and two different kinds of stimuli.

One potential mechanism by which THC during retrieval could increase false recollections is by impairing prefrontal functions (Bossong et al., 2012a, 2012b), including retrieval monitoring processes that help to suppress false recollections for words and pictures (Gallo, 2006). For example, THC is known to enhance mental imagery (Ames, 1958; Tart, 1970) and processing fluency (Morgan et al., 2010; Schafer et al., 2012), which together can result in false recollections when retrieval monitoring fails (Doss, Bluestone, & Gallo, 2016). A broad impairment of prefrontal monitoring processes also might explain why THC increased false alarms for both critical lures and unrelated lures in the DRM task.

Our finding that THC at retrieval, like some other recreational drugs (dextroamphetamine, Ballard et al., 2014; MDMA, Doss et al., 2018), tended to disproportionately increase emotionally positive false memories is consistent with work showing that positive compared to negative memories are more susceptible to distortion (Bohn & Berntsen, 2007; Kensinger & Schacter, 2006; Levine & Bluck, 2004). It is possible that all of these drugs bias retrieval toward positive false memories because they impact the ventral striatum, a region involved in both positive memory retrieval (Speer et al., 2014) and general drug effects (Yager et al., 2015). Alternatively, drug effects on positive false memories could be related to a mood congruent response bias. Such a drug-induced increase in the processing of positive memories could influence the likelihood of using drugs even if users lack awareness of such an effect.

These findings have potential implications for the widespread use of cannabis, including its medical use. First, all users should be aware that single doses of this drug can distort episodic memory retrieval at a level that may not be perceptible to the user. Increased false recollections may contribute to cannabis' known relationship with psychosis (Radhakrishnan, Wilkinson, & D'Souza, 2014). Second, these findings may be especially important for PTSD. Individuals with PTSD are predisposed to having distorted memories (Strange & Takarangi, 2015), and susceptibility to false memory formation is a complication in psychotherapy (McNally, 2003), especially when adjunct drugs have been involved (Piper et al., 1993). Our findings, therefore, implicate a potential constraint on the use of THC during psychotherapy. Notably, the finding that THC did not suppress the retrieval of negative memories is at odds with the proposal that cannabis can reduce emotional reactivity to negative memories and PTSD symptomology more generally (Tull, McDermott, & Gratz, 2016; Yarnell, 2015), though THC might impact emotional processing in ways not studied here. As cannabis becomes increasingly accepted for its potentially beneficial properties, rigorous investigations of the impact of THC and other cannabinoids on memory and cognition will be important for harm reduction approaches, as well as understanding the factors that influence drug use.

# Chapter 3:

# MDMA Impairs Both the Encoding and Retrieval of Emotional Recollections

In addition to THC, another drug that is currently being explored for its clinical potential in the treatment of PTSD is MDMA. In spite of having stimulant effects, MDMA has been shown to be amnestic when administered prior to encoding (e.g., Kuypers & Ramaekers, 2005). However, as was the case with cannabis and THC, previous work did not properly isolate MDMA's effect to encoding or retrieval because MDMA was administered prior to encoding and memory was tested soon after encoding when drug effects persisted through retrieval. Therefore, in the current experiment, I tested MDMA on either the encoding or retrieval of emotional episodic memories. This procedure allowed me to examine whether like other psychoactive drugs, MDMA during encoding would have emotionally selective effects and MDMA during retrieval would increase false memories.

Another goal of this study was to see which episodic memory processes are targeted by MDMA. It might not be appropriate to dampen all memory processes when using a drug for psychotherapy, as this could perturb new learning. In an effort to pursue this goal, I implemented a modeling procedure to dissociate two episodic memory processes, recollection and familiarity. (I was unable to apply this procedure in the last chapter due to the high incidence of high confidence false alarms.) Whereas recollection involves recalling details and associations, familiarity is thought to be more of a feeling of knowing that an event has occurred in the absence of contextual details. Altering recollection may especially be important for treating PTSD, as flashbacks are thought to be aberrant negative recollections. To anticipate the findings,

MDMA at encoding or retrieval only dampened emotional recollections. In contrast, as is found in Chapter 4, alcohol and other $GABA_A$ PAMs administered at encoding impair both recollection and familiarity. These qualitative differences between these different drugs might help explain why some amnestic drugs are better posited as adjuncts to psychotherapy for the treatment of PTSD.

## Background

Recent findings from clinical and basic research suggest that the stimulant-psychedelic-entactogen ±3,4-methylenedioxymethamphetamine (MDMA) may specifically modulate emotional processing in humans. MDMA has reemerged as a potential treatment of posttraumatic stress disorder (PTSD; Sessa, 2016) possibly due to its prosocial effects (Bershad et al., 2016), which may make it easier for patients to discuss traumatic events. Alternatively, MDMA may modify traumatic memories themselves, consistent with the characterization of PTSD as a disorder of emotional memory (Rubin et al., 2008). Patients with PTSD exhibit hypervigilance to threat and a hyperresponsive amygdala (Rauch et al., 2006) while in neurotypical populations, MDMA attenuates the detection of threat-related emotional faces (Hysek et al., 2014) and amygdalar activation (Bedi et al., 2009). Together, such findings implicate that MDMA may alter emotional memory.

To date, there have been no studies on how MDMA might affect emotional episodic memory, but there is some evidence that MDMA impairs memory for emotionally neutral information. MDMA worsens memory when it is administered before the encoding of neutral verbal stimuli (Kuypers & Ramaekers, 2005), and this effect can be reversed by blocking the 5-$HT_{2A}$ receptor (van Wel et al., 2011), a site that binds psychedelic drugs and differentiates MDMA from classic stimulants. However, these studies tested memory shortly after encoding

while participants were still intoxicated, making it difficult to determine whether MDMA affected encoding or retrieval.

Although prior work with MDMA has revealed a potentially amnestic effect on emotionally neutral memories, MDMA also has a stimulating effect, suggesting that its profile for emotional episodic memories may be more complex. Specifically, we have found that classic stimulants (e.g., dextroamphetamine) have greater specificity for enhancing memories with emotional content (Ballard et al., 2013). Both dextroamphetamine and MDMA drive the noradrenergic system, which is thought to support emotional memory enhancements (Mather et al., 2016). It may be that any amnestic effects of MDMA on emotional memory are negated by its effects on the noradrenergic system.

MDMA may also alter memory during retrieval, independently of its potential encoding effects. Although the effects of MDMA on episodic memory retrieval have not been tested, there is evidence that MDMA enhances subjective vividness and positivity ratings of positive autobiographical memories while reducing negativity ratings of negative autobiographical memories (Carhart-Harris et al., 2014). In this way, MDMA may have a similar effect on retrieval as dextroamphetamine, which increases memory errors and recall of positively valenced words (Ballard et al., 2014). However, there may again be differences between MDMA and classic stimulants. In mice, MDMA reduces freezing when a fear memory is recalled during extinction (Young et al., 2015), whereas dextroamphetamine does not reduce conditioned freezing during fear extinction (Carmack et al., 2010). These findings suggest that MDMA may have specific impact on the retrieval of emotional memory representations.

The present study sought to disentangle the effects of MDMA on the encoding and retrieval of negative, neutral, and positive memory. Additionally, we sought to distinguish the

MDMA effects on two components of episodic memory retrieval: recollection and familiarity. Recollection is characterized by the retrieval of specific details associated with a prior event and is known to be hippocampally-dependent, whereas familiarity is the feeling of knowing an event has occurred without the recollection of specific details and is thought to be cortically-dependent (Yonelinas, 2002). PTSD patients exhibit abnormal hippocampal structure (Smith, 2005) and function (Brohawn et al., 2010) and possess vivid recollections of traumatic events. These observations, combined with the fact that emotion specifically enhances recollection (Phelps & Sharot, 2008), suggest that the clinical efficacy of MDMA may be related to its effects on emotional recollection. Therefore, we predicted that MDMA would attenuate both the encoding and retrieval of recollection-based emotional memory.

## Methods

### Participants

Sixty healthy participants (20 per group, 50% males, 18-34 years) were recruited. Potential participants underwent a physical examination and an electrocardiogram, provided detailed information on current and lifetime drug use, and were screened by trained clinical psychologists using a semi-structured psychiatric interview on average 17 weeks before the first experimental session. Exclusion criteria included current Axis I DSM-IV disorder, including substance dependence, >5 cigarettes per day, history of psychosis or mania, less than a high school education, lack of English fluency, a body mass index outside 19-30 $kg/m^2$, high blood pressure (>140/90), abnormal electrocardiogram, daily use of any medication other than birth control, pregnancy, or lactating. Participants were eligible if they reported 4-40 past uses of MDMA with no adverse events. Women not taking hormonal contraceptives were tested during

their follicular phase because hormonal fluctuations can influence responses to stimulants (White et al., 2002). There were no group differences in participant demographics (Table 6).

| | *Placebo* | *MDMA at Encoding* | *MDMA at Retrieval* |
|---|---|---|---|
| *Female/male* | 10/10 | 10/10 | 10/10 |
| *Age (years)* | 23.85 (.34) | 24.90 (.21) | 22.45 (.10) |
| *Education (years)* | 15.10 (.11) | 15.3 (.09) | 14.85 (.08) |
| *BMI* | 22.62 (.11) | 24.37 (.16) | 23.32 (.13) |
| *Race* | | | |
| Caucasian | 45% | 55% | 55% |
| Black | 20% | 5% | 5% |
| Asian | 5% | 25% | 15% |
| Other (includes multiracial) | 30% | 15% | 25% |
| *Current Drug Use* | | | |
| Caffeinated drinks per day | 1.67 (.05) | 1.04 (.04) | 1.24 (.06) |
| Cigarettes per day | 1.14 (.10) | .69 (.06) | .74 (.08) |
| % Smokers | 55% | 40% | 50% |
| Alcoholic drinks per week | 4.13 (.11) | 3.80 (.09) | 3.80 (.12) |
| *Lifetime Drug Use (at least once)* | | | |
| Marijuana | 100% | 100% | 100% |
| Sedatives | 65% | 65% | 50% |
| Stimulants | 100% | 90% | 80% |
| Opiates | 80% | 85% | 75% |
| Hallucinogens | 80% | 95% | 85% |
| *Lifetime uses of MDMA* | 11.50 (.41) | 15.95 (.47) | 10.98 (.41) |
| *Last use of MDMA (in years)* | 1.26 (.40) | 1.05 (.35) | .80 (.20) |

**Table 6.** Demographic data of groups in Chapter 3. Non-percent values are mean and SEM in parentheses. Lifetime drug use refers to recreational use only.

Qualifying participants attended an orientation session to give consent and practice study tasks. To minimize expectancy, participants were informed that they could receive a stimulant, sedative, cannabinoid, or placebo. Participants were instructed to consume their normal amounts of caffeine and nicotine before sessions but to abstain from using alcohol, prescription drugs (except contraceptives), and over-the-counter drugs for 24 hours before the sessions, marijuana for 72 hours before the sessions, and other illicit drugs for 48 hours before the sessions (due to faster clearance). Participants were notified that there would be drug tests and that they would be rescheduled if they tested positive for any recent drug use at the first session and cancelled from the study if they tested positive at the second session with only partial compensation. Participants were advised to get their normal amounts of sleep and not to eat for two hours before each session. Following completion of the study, participants were fully debriefed and monetarily compensated. The study took place at the University of Chicago Medical Center and was approved by the Institutional Review Board.

**Drug**

MDMA (1.0 mg/kg) was prepared for each participant by the hospital pharmacist. The powder form of the drug was obtained from Dr. David Nichols of Purdue University and placed in opaque size 00 capsules with dextrose filler. Placebo capsules contained only dextrose. This is a moderate dose of MDMA relative to doses that previously affected memory (75 mg in Kuypers & Ramaekers, 2005).

**Design**

Subjects were randomly assigned to one of three groups, one that received MDMA during encoding and placebo during retrieval (Encoding), one that received MDMA during retrieval and placebo during encoding (Retrieval), and one that received placebo during both

phases (Placebo). All participants attended two sessions separated by 48 hours: an encoding session for studying stimuli and a retrieval session for testing memory. Besides the drug manipulation, the procedure for all groups was identical and double-blinded. All sessions began in the morning.

**Stimuli**

Stimuli consisted of 180 images from the International Affective Picture Set (IAPS; Lang et al., 2008) and 2-3 word labels (e.g., "dirty toilet", "box of tissues", "chocolate candy bar") describing these images. The images included emotionally negative, neutral, and positive pictures and were split into two comparable sets for counterbalancing studied and nonstudied items across participants. These pictures had the following mean (*SD*) normed valences and arousals, respectively: Set A: negative 3.09 (.51) and 5.21 (.66), neutral 5.15 (.43) and 3.51 (.68), positive 7.10 (.52) and 5.00 (.79). Set B: negative 3.14 (.50) and 5.21 (.65), neutral 5.10 (.55) and 4.12 (.90), positive 7.08 (.53) and 5.17 (.77).

**Procedure**

On the morning of experimental sessions, participants first completed compliance measures including breath alcohol level (Alco-sensor III, Intoximeters, St. Louis, MO), a urine drug test (ToxCup, Branan Medical Co. Irvine, CA), and a pregnancy test (females only; Aimstrip, Craig Medical, Vista, CA), as well as baseline cardiovascular and mood measures. Participants then consumed a capsule and completed cardiovascular and mood measures every 30 minutes for the next 90 minutes. Participants were provided with magazines and music in furnished rooms. They were not allowed to eat, sleep, or work, and they had no access to cell phones or Internet. Upon completing tasks, participants watched a movie.

During the encoding session, 90 minutes post-capsule ingestion, participants viewed all 180 labels, half of which were followed by the corresponding picture. For each label, participants rated on a 5-point scale how much they would like to see the corresponding picture. When a picture was presented, participants rated its positivity and negativity on a 5 × 5 grid with positivity and negativity on orthogonal axes. After this valence rating, they rated the picture's arousal on a five-point scale. This phase was self-paced and lasted approximately 30 minutes. There were no group differences in liking ratings of labels and valence/arousal ratings of images, so these will not be reported.

During the retrieval session, 90 minutes post-capsule ingestion, participants were given two surprise memory tests, a cued recollection test and a picture recognition test. For the cued recollection test, participants were presented with each label and asked whether they had seen the corresponding picture. Afterward, they rated their confidence on a five-point scale and were encouraged to use the entire scale. After the cued recollection test, participants were presented with each picture and had to decide if it had been seen. When a picture was recognized, they were asked if they "remember" the picture or they simply "know" it was presented (Yonelinas, 2002). Participants were instructed that they should give a "remember" response when they could recollect associated details from the event, such as thoughts during its presentation, and they should give a "know" response when they simply knew that a picture had been presented without recollecting specific details. Both memory tests were self-paced and together lasted approximately 45 minutes.

**Dependent Measures**

Several measures were obtained to monitor expected drug effects (Table 7). Heart rate and blood pressure were measured using a portable blood pressure monitor (A&D Medical/Life

Source, San Jose, CA). Mood measures included the Profile of Mood States (McNair, Lorr, & Droppleman, 1971), the Visual Analog Scales (Folstein & Luria, 1973), the Drug Effects Questionnaire (Morean et al., 2013), and an End of Session Questionnaire. The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971) consists of 72 adjectives on which individuals report their current mood on a 5-point scale from 0 (not at all) to 4 (extremely). Eight clusters of items are separated empirically by factor analysis (friendliness, anxiety, elation, anger, fatigue, depression, confusion, and vigor). The Visual Analog Scales (VAS; Folstein & Luria, 1973) consists of thirteen adjectives used to assess individual dimensions of subjective mood – anxious, stimulated, sedated, elated, insightful, sociable, confident, lonely, playful, dizzy, loving, friendly, restless. Participants rated their responses on 100 mm sliding scales ranging from 'not at all' to 'extremely.' The Drug Effects Questionnaire (DEQ; Morean et al., 2013) consists of five questions concerning current drug effects – how much participants feel a drug effect, like the effect, dislike the effect, feel high, and want more of the drug. Participants rated their responses on 100 mm sliding scales from 'not at all/neutral' to 'very much.' Participants were instructed to select 'not at all/neutral' if they had not yet received a capsule. The End of Session Questionnaire (ESQ) asks participants what class of drugs they thought they received at the end of each session.

| | *Session 1* | | | *Session 2* | | |
|---|---|---|---|---|---|---|
| | Placebo | MDMA at Encoding | MDMA at Retrieval | Placebo | MDMA at Encoding | MDMA at Retrieval |
| *Heart Rate* | -7.70 (1.09) | **6.20 (1.87)** | -3.20 (1.98) | -3.80 (1.67) | -9.60 (1.65) | **6.35 (1.78)** |
| *Systolic BP* | -3.55 (2.32) | **16.55 (2.17)** | .15 (2.02) | -1.95 (1.48) | -2.75 (1.90) | **12.65 (6.10)** |
| *Diastolic BP* | -1.15 (2.76) | **8.85 (2.07)** | .85 (2.22) | -3.00 (1.23) | -1.30 (1.95) | **11.80 (2.21)** |
| *POMS* | | | | | | |
| Friendliness | -2.45 (0.61) | -1.35 (1.57) | -4.40 (1.00) | -1.95 (.63) | -2.30 (.92) | **.60 (1.07)** |
| Anxiety | -.10 (.51) | **2.15 (.92)** | -.50 (.77) | .65 (.39) | .05 (.15) | **6.85 (1.81)** |
| Elation | -1.40 (.61) | -.30 (1.26) | -2.00 (.62) | -1.50 (.67) | -1.35 (2.43) | **2.25 (.88)** |
| Anger | -.60 (.36) | -.1 (.42) | -2.45 (.86) | -.40 (.17) | .05 (.22) | **1.25 (.79)** |
| Fatigue | .65 (.74) | .45 (1.21) | -.15 (.73) | .30 (.46) | .8 (.49) | -.25 (.64) |
| Depression | -.55 (.51) | 1.10 (.72) | -1.90 (1.09) | -.30 (.33) | .05 (.22) | 2.20 (1.37) |
| Confusion | .10 (.52) | **2.30 (.75)** | -.25 (.63) | .25 (.26) | .1 (.42) | **2.85 (1.04)** |
| Vigor | -3.10 (.81) | .00 (2.14) | -4.30 (1.20) | -1.85 (1.11) | -2.60 (.75) | **3.60 (1.85)** |
| *VAS* | | | | | | |
| Anxious | -1.35 (1.63) | 8.40 (5.14) | -2.00 (4.35) | -1.10 (2.68) | -2.25 (1.44) | **25.80 (5.55)** |
| Stimulated | 2.40 (4.62) | **27.10 (7.01)** | -1.90 (4.45) | .35 (4.01) | -2.85 (1.93) | **40.60 (6.36)** |

**Table 7.** Physiological and mood measures in Chapter 3. Mean (SEM) values are changes from pre-capsule to immediately before encoding (session 1) and retrieval (session 2). Bold values indicate significant differences ($p < .05$) between drug and Placebo groups (*t* test; see SOM for statistics). POMS = Profile of Mood States, VAS = Visual Analog Scales, DEQ = Drug Effects Questionnaire, ESQ = End of Study Questionnaire.

| | | | | | | |
|---|---|---|---|---|---|---|
| Sedated | 18.40 (6.21) | 16.00 (7.47) | 12.25 (4.76) | 6.75 (6.03) | 9.60 (3.19) | -.10 (5.17) |
| Elated | .40 (3.79) | 11.80 (6.05) | -4.70 (3.48) | 1.85 (3.61) | -.85 (1.47) | **16.80 (5.62)** |
| Insightful | .05 (4.44) | **12.25 (4.00)** | -2.45 (4.29) | .45 (2.33) | 1.90 (2.85) | **28.80 (5.05)** |
| Sociable | -4.60 (4.38) | 2.10 (5.09) | -5.60 (4.49) | -2.20 (3.07) | -2.00 (3.86) | **15.00 (6.94)** |
| Confident | -6.05 (2.18) | -7.10 (4.83) | -5.15 (3.20) | -.75 (2.89) | -1.15 (4.21) | 13.15 (7.84) |
| Lonely | 4.90 (4.35) | 9.60 (4.67) | -1.30 (3.34) | .95 (1.75) | 4.60 (2.91) | 12.30 (7.10) |
| Playful | -7.65 (4.56) | 2.50 (5.69) | -.95 (4.30) | 3.15 (3.39) | -3.30 (2.83) | 17.25 (7.92) |
| Dizzy | 2.75 (3.14) | 6.30 (4.93) | -1.65 (1.14) | 5.90 (3.64) | -.05 (1.99) | 17.60 (5.30) |
| Loving | -11.10 (4.87) | **13.40 (5.13)** | -.60 (4.33) | -2.70 (2.10) | -1.20 (2.77) | **16.20 (5.52)** |
| Friendly | -8.95 (2.08) | **2.70 (4.33)** | -9.55 (4.06) | -1.10 (2.79) | -5.35 (3.12) | 7.80 (6.98) |
| Restless | 5.60 (3.61) | 15.25 (6.11) | 10.00 (3.77) | 4.60 (4.04) | 11.00 (5.18) | **31.85 (8.57)** |
| | | | | | | |
| *DEQ* | | | | | | |
| Feel drug effect | 21.50 (4.70) | **50.60 (5.60)** | 11.30 (3.69) | 14.15 (5.02) | 6.40 (2.52) | **58.75 (5.75)** |
| Like drug effect | 34.40 (7.56) | **57.20 (7.24)** | 21.45 (6.94) | 18.05 (5.45) | 8.95 (3.94) | **62.55 (6.57)** |
| Dislike drug effect | 7.60 (2.47) | **19.25 (4.58)** | 3.70 (1.60) | 7.95 (2.88) | 2.90 (1.16) | **21.40 (5.41)** |
| Feel high | 17.40 (4.51) | **48.45 (6.96)** | 10.95 (4.06) | 11.50 (4.83) | 6.95 (3.03) | **53.25 (6.46)** |
| Want more drug | 52.20 (8.07) | 44.75 (7.53) | 36.85 (8.45) | 27.65 (5.89) | 14.85 (6.46) | **48.80 (8.08)** |
| | | | | | | |
| *ESQ (percent who guessed receiving)* | | | | | | |
| stimulant | 15% | 75% | 15% | 10% | 0% | 80% |
| sedative | 35% | 15% | 30% | 20% | 15% | 5% |
| cannabinoid | 20% | 5% | 10% | 10% | 15% | 10% |
| placebo | 25% | 5% | 45% | 60% | 70% | 5% |

**Table 7** continued.

For the cued recollection test (Table 8), hit and false alarm rates were calculated for each valence in each subject. False alarms were subtracted from hits to compute memory accuracy. Finally, high confidence hits, false alarms, and accuracy were calculated by only including responses with the top two levels of confidence.

| | *Placebo* | | | *MDMA at Encoding* | | | *MDMA at Retrieval* | | |
|---|---|---|---|---|---|---|---|---|---|
| | Negative | Neutral | Positive | Negative | Neutral | Positive | Negative | Neutral | Positive |
| Hits | .71 (.04) | .60 (.04) | .62 (.05) | .69 (.03) | .59 (.03) | .63 (.03) | .72 (.03) | .60 (.04) | .63 (.03) |
| FAs | .10 (.02) | .09 (.02) | .12 (.01) | .10 (.02) | .11 (.02) | .13 (.02) | .15 (.04) | .13 (.04) | .19 (.03) |
| Accuracy | .61 (.04) | .51 (.04) | .50 (.04) | .59 (.03) | .48 (.03) | .49 (.03) | .58 (.04) | .47 (.04) | .45 (.03) |
| Hi Conf Hits | .54 (.05) | .42 (.04) | .44 (.05) | .48 (.04) | .37 (.03) | .37 (.04) | .55 (.04) | .44 (.04) | .44 (.04) |
| Hi Conf FAs | .02 (.01) | .01 (.00) | .03 (.01) | .02 (.01) | .01 (.01) | .03 (.01) | .05 (.02) | .05 (.03) | .07 (.02) |
| Hi Conf Acc | .52 (.05) | .41 (.04) | .42 (.05) | .46 (.04) | .35 (.03) | .34 (.03) | .50 (.04) | .39 (.04) | .37 (.03) |
| R Estimate | .40 (.05) | .28 (.05) | .31 (.04) | .25 (.05) | .25 (.03) | .21 (.04) | .33 (.05) | .26 (.06) | .27 (.04) |
| F Estimate | 1.10 (.11) | .92 (.08) | .76 (.11) | 1.26 (.09) | .89 (.09) | .97 (.09) | 1.11 (.10) | .73 (.09) | .65 (.06) |

**Table 8.** Cued recollection data in Chapter 3. Values are means with SEM in parentheses except for the R and F estimates, which are point estimates of the aggregate ROC curves and standard deviations of the bootstrapping distributions. FA = false alarm, Hi Conf = high confidence, Acc = accuracy, R = recollection, F = familiarity.

To estimate recollection and familiarity, confidence data were submitted to a dual process signal detection (DPSD) analysis (Yonelinas, 2002) using the ROC Toolbox for MATLAB (Koen et al., 2016). Confidence data were combined between "yes" and "no" responses to create a 10-point scale. The cumulative proportion of hits is plotted against the cumulative proportion of false alarms from the most stringent criterion (i.e., the proportion of hits and false alarms at the highest level of confidence) to the most liberal criterion, ending at (1,1). A receiver operator characteristic (ROC) curve is then fit to these points using maximum likelihood estimation. The DPSD model assumes a threshold process (recollection) can take place on some proportion of trials that is reflected by the *y*-intercept (measured as a probability). In contrast, familiarity is thought to be a signal detection process, reflected in the curvilinearity of the function (measured in *z* score units).

For the recognition test (Table 9), hits, false alarms, and accuracy were calculated, and recollection and familiarity estimates were derived from the independence remember/know (IRK) procedure (Yonelinas, 2002). Recollection accuracy was measured by:

$$p(\text{"remember"}|\text{old}) - p(\text{"remember"}|\text{new})$$

Because a "know" response is the probability of familiarity in the absence of recollection, a correction was made to avoid underestimation. Familiarity accuracy is measured as:

$$\frac{p(\text{"know"}|\text{old})}{1 - p(\text{"remember"}|\text{old})} - \frac{p(\text{"know"}|\text{new})}{1 - p(\text{"remember"}|\text{new})}$$

In order to avoid negative familiarity estimates and dividing by 0, floor and ceiling hits and false alarms were replaced by .5/*N* and 1 - .5/*N*, respectively, where *N* is the maximum number of hits and false alarms that could be made (Macmillan & Creelman, 1991). Note that each of these estimates corrects for subjective responses to nonstudied items, thereby estimating recollection and familiarity unique to items studied in the encoding phase.

| | *Placebo* | | | *MDMA at Encoding* | | | *MDMA at Retrieval* | | |
|---|---|---|---|---|---|---|---|---|---|
| | Negative | Neutral | Positive | Negative | Neutral | Positive | Negative | Neutral | Positive |
| Hits | .89 (.02) | .89 (.03) | .89 (.03) | .87 (.02) | .89 (.02) | .87 (.03) | .90 (.02) | .92 (.02) | .90 (.02) |
| FAs | .05 (.01) | .05 (.01) | .07 (.01) | .05 (.01) | .07 (.01) | .07 (.02) | .09 (.03) | .08 (.03) | .12 (.03) |
| Accuracy | .84 (.02) | .84 (.03) | .83 (.03) | .82 (.02) | .82 (.02) | .80 (.03) | .81 (.03) | .84 (.03) | .78 (.04) |
| R Hits | .71 (.03) | .70 (.03) | .67 (.03) | .60 (.04) | .64 (.04) | .55 (.04) | .67 (.04) | .70 (.03) | .66 (.03) |
| R FAs | .02 (.00) | .02 (.00) | .02 (.00) | .02 (.00) | .02 (.00) | .02 (.00) | .03 (.01) | .02 (.00) | .03 (.01) |
| R Acc | .69 (.03) | .68 (.03) | .65 (.03) | .58 (.04) | .62 (.04) | .53 (.04) | .64 (.04) | .69 (.03) | .63 (.03) |
| IRK F Hits | .66 (.06) | .66 (.07) | .70 (.07) | .66 (.04) | .73 (.04) | .75 (.05) | .70 (.05) | .74 (.05) | .72 (.05) |
| IRK F FAs | .05 (.01) | .05 (.01) | .06 (.01) | .05 (.01) | .07 (.01) | .07 (.02) | .08 (.03) | .09 (.03) | .11 (.03) |
| IRK F Acc | .61 (.06) | .62 (.07) | .63 (.07) | .61 (.05) | .66 (.04) | .67 (.05) | .62 (.05) | .66 (.06) | .61 (.06) |

**Table 9.** Recognition data in Chapter 3. Values are means with SEM in parentheses. FA = false alarm, Hi Conf = high confidence, Acc = accuracy, R = recollection, IRK = independence remember/know, F = familiarity.

### Statistical Analysis

Encoding and Retrieval groups were compared separately to the Placebo group. Cued recollection hits, false alarms, accuracy, and high confidence measures were submitted to 2 (group) × 3 (valence) ANOVAs. Recognition hits, false alarms, accuracy, recollection estimates, and familiarity estimates were also submitted to 2 × 3 ANOVAs. When sphericity was violated, a Greenhouse-Geisser correction was applied to the degrees of freedom. Pairwise comparisons were conducted with *t* tests.

Estimates of recollection and familiarity derived from ROC curves can be calculated individually for each participant (e.g., Koen et al., 2013). However, because the number of studied and nonstudied items per condition was low (i.e., 30 each compared to 60-150 in Koen et al.), confidence data were collapsed across participants to generate aggregate ROC curves. Parameter reliability was assessed via non-parametric bootstrapping. For each condition, distributions of recollection and familiarity estimates were generated by randomly sampling twenty subjects with replacement and running an ROC analysis (10,000 iterations). Pairwise comparisons were made by subtracting distributions and calculating what proportion of the difference distribution lay above 0. Confidence intervals for the difference of two means were obtained from the 2.5% and 97.5% quantiles of the difference distributions.

## Results

### Drug Effects on Cardiovascular and Subjective Measures

Participants who received MDMA displayed many of its typical effects in comparison to the placebo group (Table 7). Heart rate (Placebo vs. Encoding: $t(38) = 6.413$, $p < .001$, $d = 2.028$; Placebo vs. Retrieval: $t(38) = 4.159$, $p < .001$, $d = 1.315$), systolic blood pressure (Placebo vs. Encoding: $t(38) = 6.321$, $p < .001$, $d = 1.999$; Placebo vs. Retrieval: $t(38) = 2.326$, $p = .025$, $d =$

.736), and diastolic blood pressure (Placebo vs. Encoding: $t(38) = 2.899$, $p = .006$, d = .917; Placebo vs. Retrieval: $t(38) = 5.858$, $p < .001$, $d = 1.852$) were all increased by MDMA in the first session for the Rncoding group and second session for the Retrieval group.

On the POMS, in the Encoding group, MDMA increased the factors anxiety ($t(38) = 2.134$, $p = .039$ $d = .675$) and confusion ($t(38) = 2.632$, $p = .012$, $d = .832$). In the Retrieval group, MDMA increased the factors friendliness ($t(38) = 2.054$, $p = .047$, $d = .649$), anxiety ($t(38) = 3.356$, $p = .002$, $d = 1.061$), elation ($t(38) = 3.384$, $p = .002$, $d = 1.070$), anger ($t(38) = 2.040$, $p = .048$, $d = .645$), confusion ($t(38) = 2.427$, $p = .020$, $d = .767$), and vigor ($t(38) = 3.118$, $p = .003$, $d = .986$).

On the VAS, in the Encoding group, MDMA increased feeling stimulated ($t(38) = 2.942$, $p = .006$, $d = .930$), insightful ($t(38) = 2.040$, $p = .048$, $d = .645$), loving ($t(38) = 3.463$, $p = .001$, $d = 1.095$), and friendly ($t(38) = 2.428$, $p = .020$, $d = .768$). In the Retrieval group, MDMA increased feeling anxious ($t(38) = 4.368$, $p < .001$, $d = 1.381$), stimulated ($t(38) = 5.352$, $p < .001$, $d = 1.692$), elated ($t(38) = 2.237$, $p = .031$, $d = .219$), insightful ($t(38) = 5.098$, $p < .001$, $d = 1.612$), sociable ($t(38) = 2.267$, $p = .029$, $d = .013$), loving ($t(38) = 3.200$, $p = .003$, $d = 1.012$), and restless ($t(38) = 2.876$, $p = .007$, $d = .308$).

On the DEQ, MDMA increased feeling the drug effect (Placebo vs. Encoding: $t(38) = 3.983$, $p < .001$, $d = 1.260$; Placebo vs. Retrieval: $t(38) = 5.844$, $p < .001$, $d = 1.848$), liking the drug effect (Placebo vs. Encoding: $t(38) = 2.179$, $p = .036$, $d = .689$; Placebo vs. Retrieval: $t(38) = 5.210$, $p < .001$, $d = 1.648$), disliking the drug effect (Placebo vs. Encoding: $t(38) = 2.239$, $p = .031$, $d = .708$; Placebo vs. Retrieval: $t(38) = 2.196$, $p = .034$, $d = .694$), and feeling high (Placebo vs. Encoding: $t(38) = 3.743$, $p < .001$, $d = 1.184$; Placebo vs. Retrieval: $t(38) = 5.177$, $p$

< .001, $d$ = 1.637). MDMA also increased wanting more drug in the Retrieval group ($t$(38) = 2.115, $p$ = .041, $d$ = .463).

**Cued Recollection: Placebo vs. Encoding**

Raw cued recollection performance was directly related to valence as indicated by main effects on hits ($F$(2,76) = 14.109, $p$ < .001, $\eta_p^2$ = .271) and accuracy ($F$(2,76) = 14.259, $p$ < .001, $\eta_p^2$ = .273). These main effects were due to the typical advantage for negative stimuli (Figures 4a and 4c). There was a trending main effect of valence on false alarms ($F$(2,76) = 2.488, $p$ = .090, $\eta_p^2$ = .061) due to more false alarms for positive stimuli (Figure 4b). No other main effects or interactions were found (all $Fs$ < 2.000, all $p$s > .200).

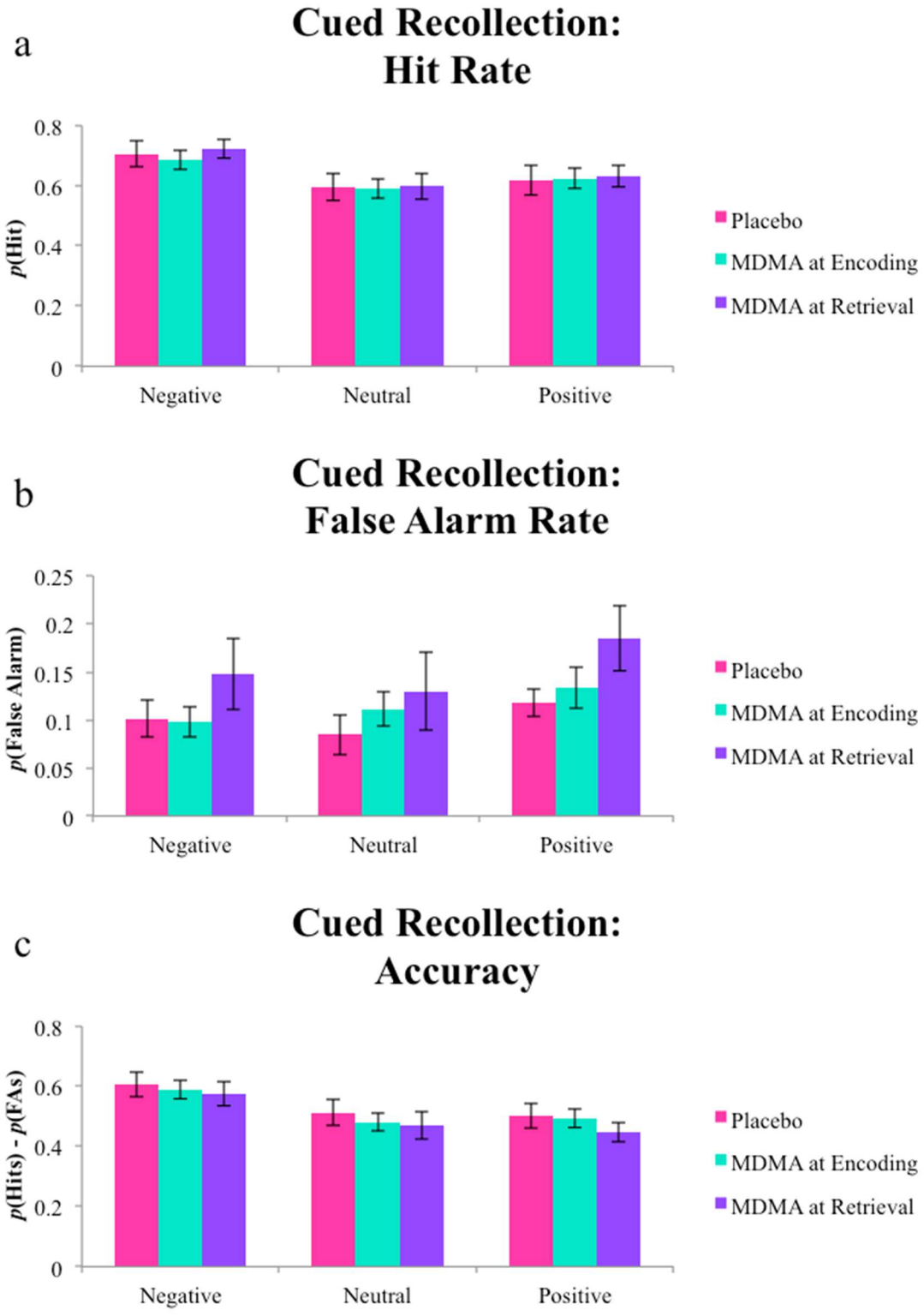


**Figure 4.** Raw performance on the cued recollection task in Chapter 3. **a.** Mean hit rates, **b.** false alarm rates, and **c.** accuracy (hit rates - false alarm rates). Error bars are SEM.

There was a main effect of valence on high confidence hits ($F(2,76) = 16.599$, $p < .001$, $\eta_p^2 = .304$) and high confidence accuracy ($F(1.669,63.427) =$ , $p < .001$, $\eta_p^2 = .287$) due to greater memory for negative material. There was also a main effect of valence on high confidence false alarms ($F(2,76) = 3.411$, $p = .038$, $\eta_p^2 = .082$) due to greater false alarms for positive pictures.

The distributions of DPSD-based recollection and familiarity estimates from the bootstrapping procedure were all normal (Figure 5). Negative (95% CI: [.004, .297], $p = .022$) and positive (95% CI: [-.008, .207], $p = .034$) recollection estimates in the Encoding group were reduced compared to the Placebo group, though the confidence interval of the difference distribution for positive recollection estimates implied a less reliable effect. The Encoding and Placebo groups did not differ on neutral recollection estimates or familiarity estimates (all $p$s > 0.100), though there was trend for greater positive familiarity estimates in the Encoding group (95% CI: [-.085, .465], $p = .078$).

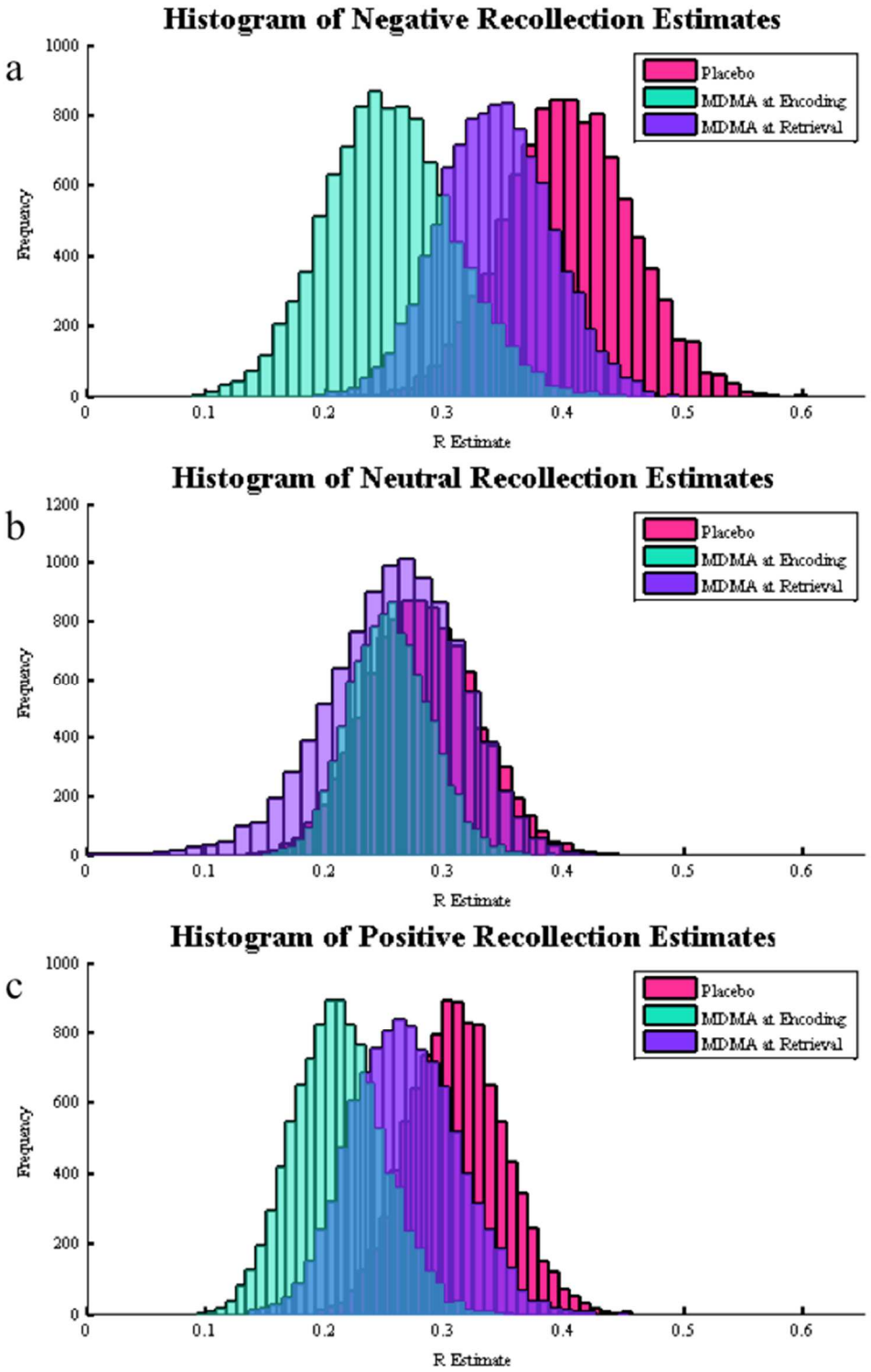


**Figure 5.** Distributions of **a.** negative, **b.** neutral, and **c.** positive dual process signal detection-based recollection estimates generated from the bootstrapping procedure on the cued recollection confidence data in Chapter 3.

**Recognition: Placebo vs. Encoding**

The ANOVAs on hits, false alarms, and accuracy from the picture recognition test were not significant (all $F$s < 1 and $p$s > .250), except for a trending effect of valence on false alarms ($F(2,76) = 2.286$, $p = .109$, $\eta_p^2 = .057$) due to greater false alarms to positive pictures.

The ANOVA on recollection estimates from the IRK procedure revealed a main effect of valence ($F(2,76) = 3.962$, $p = .007$, $\eta_p^2 = .122$) and a marginal effect of group ($F(1,38) = 5.289$, $p = .054$, $\eta_p^2 = .094$) with no interaction ($F(2,76) = 1.559$, $p = .217$). The main effect of valence was due to smaller recollection estimates for positive pictures, and the main effect of group was due to attenuated recollection in the Encoding group (Figure 6). Although the interaction was not significant, exploratory contrasts found both negative ($t(38) = 2.154$, $p = .038$, $d = .681$) and positive ($t(38) = 2.164$, $p = .037$, $d = .684$) recollection estimates to be lower in the Encoding group compared to the Placebo group with no reliable difference between neutral estimates ($t(38) = 1.079$, $p = .287$, $d = .341$), consistent with the DPSD-based recollection estimates. There were no main effects or interactions on familiarity estimates (all $F$s < 1 and all $p$s > .250).

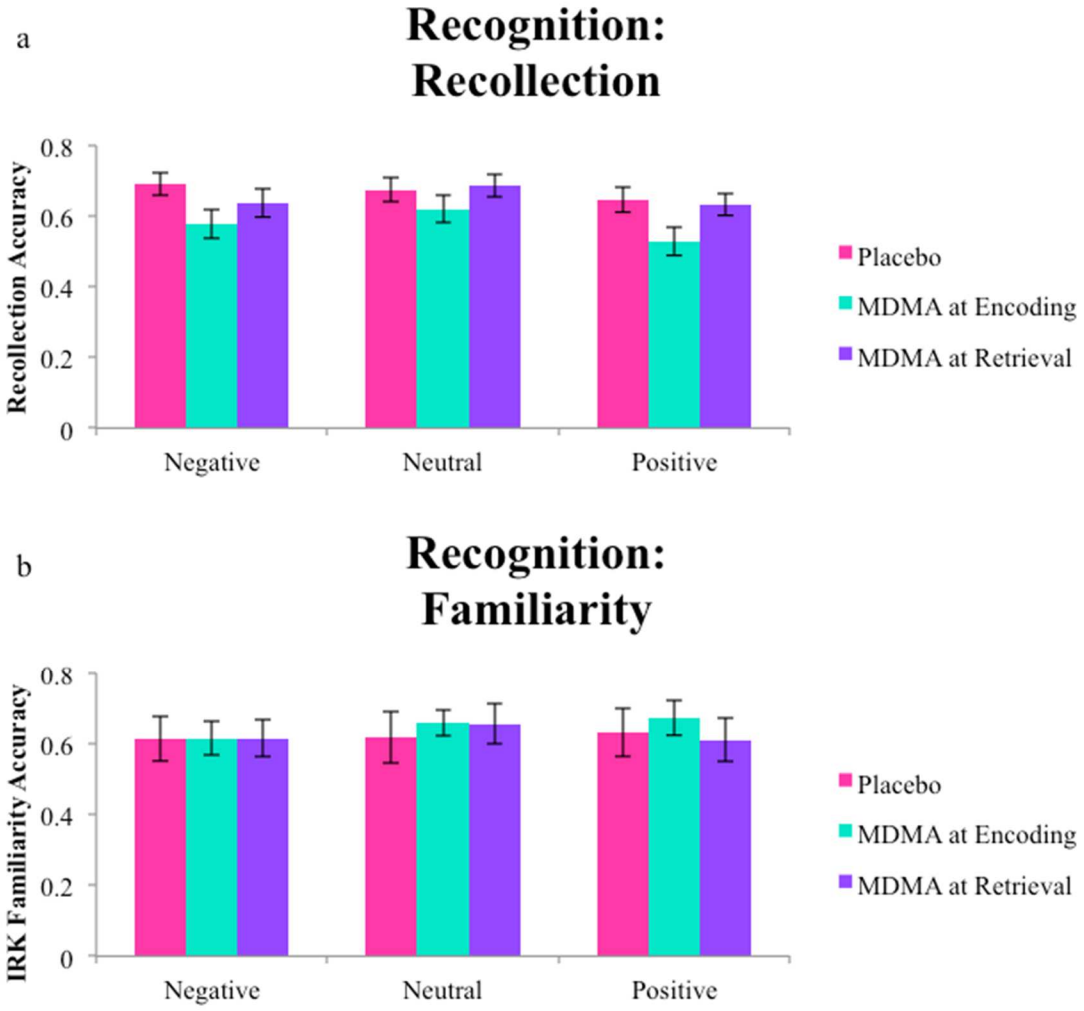


**Figure 6.** Mean independence remember/know estimates of **a.** recollection and **b.** familiarity from the recognition task in Chapter 3. Error bars are SEM.

**Cued Recollection: Placebo vs. Retrieval**

Emotional valence strongly modulated hits ($F(2,76) = 18.143$, $p < .001$, $\eta_p^2 = .323$) and accuracy ($F(2,76) = 16.417$, $p < .001$, $\eta_p^2 = .302$) such that negative pictures showed a memory advantage. Valence modulated false alarms ($F(2,76) = 4.121$, $p = .020$, $\eta_p^2 = .098$) due to more false alarms for positive stimuli. All other main effects and interactions were not statistically significant (all $F$s < 2.000, $p > .150$).

There was a main effect of valence on high confidence hits ($F(2,76) = 19.477$, $p < .001$, $\eta_p^2 = .339$) and high confidence accuracy ($F(1.737,65.994) = 18.567$, $p < .001$, $\eta_p^2 = .328$) due to better memory for negative pictures. The main effect of valence on high confidence false alarms did not reach significance ($F(2,76) = 2.136$, $p = .125$, $\eta_p^2 = .053$). However, because there was a trending main effect of group on high confidence false alarms ($F(1,38) = 2.698$, $p = .109$, $\eta_p^2 = .066$) and prior research has demonstrated that dextroamphetamine at retrieval increases memory errors (Ballard et al., 2014), we conducted exploratory contrasts between groups on high confidence false alarms. The only significant comparison was on positive stimuli ($t(19) = 2.0761$, $p = .045$, $d = .657$) such that the Retrieval group produced more high confidence false alarms for these stimuli.

Although the difference between negative recollection estimates in the Placebo and Retrieval groups was not significant (95% CI: [-.075, .198], $p = .193$), by comparison, the difference between the Encoding and Retrieval groups was also not significant (95% CI: [-.052, .224], $p = .101$). This can be seen in Figure 5a, which shows the negative recollection distribution of the Retrieval group lying in between those of the Encoding and Placebo groups. The distribution for positive recollection estimates of the Retrieval group was also in between the Placebo and Encoding groups with no difference between either of them (Figure 5c; Retrieval vs.

Placebo: 95% CI: [-.077, .157], $p$ = .235; Retrieval vs. Encoding: 95% CI: [-.124, .147], $p$ = .168). There were no differences between the Retrieval and Placebo groups for neutral recollection estimates and familiarity estimates (all *ps* > .200), though there was a trend for reduced neutral familiarity estimates in the Retrieval group (95% CI: [-.057, .421], $p$ = .066).

**Recognition: Placebo vs. Retrieval**

The ANOVA on hits comparing Placebo and Retrieval groups did not reveal any main effects or interactions (all *F*s < 1, all *p*s > .250). However, the ANOVA on false alarms revealed a main effect of valence ($F(2,76) = 4.247$, $p$ = .018 $\eta_p^2$ = .101), again explained by greater false alarms for positive pictures. Although a main effect of group did not reach significance ($F(1,38) = 2.389$, $p$ = .130, $\eta_p^2$ = .059), exploratory contrasts found that there was a trend for the Retrieval group to false alarm more to positive stimuli than the Placebo group ($t(38) = 1.816$, $p$ = .077, $d$ = .075), consistent with the high confidence false alarms on the cued recollection test, and this was not found for other valences (all *t*s < 1.500, all *p*s > .200). Finally, there was a trending main effect of valence on accuracy ($F(2,76) = 2.695$, $p$ = .074, $\eta_p^2$ = .066) explained by decreased accuracy for positive pictures, owing to the increased false alarms. No other main effects and interactions were significant (all *F*s < 1.500, all *p*s > .200).

There was a trending main effect of valence on recollection estimates ($F(2,76) = 2.651$, $p$ = .077, $\eta_p^2$ = .065) with positive recollection estimates being the smallest but no effect of group or interaction (all *F*s < 2.000, all *p*s > .150). Although there were no between-group differences, exploratory contrasts were conducted to determine consistent trends between the cued recollection and picture recognition tests, as were found among the Encoding group's analyses. These analyses found that both negative ($t(19) = 2.146$, $p$ = .045, $d$ = .480) and positive ($t(19)$ = 2.393, $p$ = .027, $d$ = .535) recollection estimates were reduced compared to neutral estimates in

the Retrieval group, but neither of these effects was found in the Placebo group (Figure 6a; neutral vs. negative: $t(38) = .566$, $p = .578$; neutral vs. positive: $t(19) = 1.163$, $p = .259$). There were no main effects or interactions on the familiarity estimates (all $F$s < 1 and all $p$s > .250).

## Discussion

We found that MDMA diminished the encoding of emotional information, both negative and positive, and this appeared to be specific to recollection, as there was no evidence for such an effect on familiarity. MDMA during retrieval tended to have subtler effects that mirrored those at encoding. These effects were found in recollection estimates produced from the DPSD analysis and the remember/know procedure, validating that MDMA weakened episodic memory representations. Although prior work suggests amnestic effects of MDMA on the encoding of neutral items (Kuypers & Ramaekers, 2005), our study better isolated encoding and showed effects largest on emotional material.

Our finding that MDMA appeared to have a stronger effect on emotional memory is consistent with previous work demonstrating emotionally specific encoding effects of other drugs (e.g., alcohol, Weafer et al., 2016; dextroamphetamine and Δ9-tetrahydrocannabinol, Ballard et al., 2013; ketamine, Becker et al., 2017). Alcohol and THC at encoding diminish both negative and positive memory, and dextroamphetamine at encoding enhances both negative and positive memory. These effects of dextroamphetamine are particularly interesting in light of our results with MDMA. In spite of their similar pharmacological profile and subjective effects, MDMA and dextroamphetamine have opposite effects on emotional memory, potentially because MDMA's defining effects on synaptic serotonin or 5-$HT_{2A}$ receptor stimulation oppose its stimulant effects.

MDMA at retrieval had weak effects, but the Retrieval group's data did not completely mimic those of the Placebo group. For example, emotional recollection estimates from the cued recollection test were in between the Placebo and Encoding groups, suggesting slightly impaired retrieval of emotional information under MDMA. Another trend of MDMA on memory retrieval was a tendency to increase false alarms similar to dextroamphetamine (Ballard et al., 2014). The trends with MDMA on false alarms were most apparent for positive pictures, especially high confidence false alarms on the cued recollection test. Related to this finding, higher doses of MDMA (100 mg or 1.5 mg/kg) have been shown to enhance visual imagery for positive autobiographical memories (Carhart-Harris et al., 2014) and processing fluency for emotionally positive words (Baggott et al., 2015). Therefore, MDMA during retrieval may have enhanced visual imagery and processing fluency of positive items, processes that recently have been shown to drive false recollections of pictures in other work (Doss et al., 2016).

Returning to the significant encoding effects, whereas MDMA-induced decreases in the recollection of negative information speak to its potential role as an adjunct to psychotherapy, the amnestic effects on positive recollection may interfere with its therapeutic value. There is a high comorbidity for depression in PTSD (Campbell et al., 2007), and depression has been associated with a deficit in memories for positive experiences (Dillon, 2015). Therefore, caution may be warranted when considering MDMA-assisted psychotherapy for PTSD patients with comorbid depression.

A notable observation in this study was MDMA did not affect raw proportions of hits or memory accuracy on the cued recollection test, which was designed to objectively assess the recollection of pictures. However, our measures of recollection based on the DPSD model and IRK procedure indicated that MDMA significantly impacted the recollection of emotional

memories. These different patterns may relate to the distinction between the number of events that can be successfully recollected, on the one hand, and the amount of vividness or precision of recollected details associated with these retrieved events on the other hand (e.g., quantity vs. quality, Scimeca et al., 2011; success vs. precision, Harlow & Yonelinas, 2016). In this light, our findings suggest that MDMA affected the recollection of details associated with emotional events but not necessarily the overall ability to recollect the occurrence of an emotional event.

The idea that MDMA alters the recollection of details associated with emotional events but not memory for the occurrence of the event may have important clinical implications. To the extent that memory retrieval is required to trigger reconsolidation (Kroes et al., 2016) and the encoding of new information is required to alter a memory trace (Sevenster et al., 2013), a strong amnestic effect may not be desirable for a therapeutic agent. PTSD is associated with memory impairments (Johnsen & Asbjørnsen, 2008), so any additional amnestic effect that precludes successful encoding and retrieval could actually hinder psychotherapy. Nevertheless, abolishing the precise details of traumatic memories, weakening their associations, or re-encoding these memories with novel, less emotional associations may be advantageous for preventing generalizations of fear to innocuous stimuli (i.e., second-order conditioning, Wessa & Flor, 2007). Such effects could also prevent the incorporation of trauma-related information when thinking about the future (Brown et al., 2013). Future work should explore the precise modifications MDMA has on memory, whether higher doses may be more effective at producing such modifications, and how these modifications compare to other drug-induced memory distortions.

# Chapter 4:

# Alcohol Impairs Encoding and Facilitates Consolidation of Both Recollection and Familiarity in Episodic Memory

In a previous study by our group, alcohol impaired the encoding and enhanced the consolidation of memory on a cued recollection task (Weafer, Gallo, & de Wit, 2016). These encoding effects were larger for emotional memory, similar to the effect of MDMA at encoding described in the previous chapter, and these consolidation effects were larger for neutral memories. Whereas the former effect was consistent with previous work, the latter effect was not. As discussed in Chapter 1, this may be because of the delay between encoding and retrieval.

The primary goal of the study reported in this chapter was to distinguish the amnestic effects of alcohol and other $GABA_A$ PAMs, drugs abused and prescribed in PTSD, from MDMA, a drug being explored to treat PTSD. To achieve this goal, I reanalyzed Weafer et al. (2016) using the dual process signal detection procedure from the last chapter in order to identify recollection and familiarity effects. I also applied the independence remember/know procedure that we used in Chapters 2 and 3 to the results of 11 previous studies that administered $GABA_A$ PAMs prior to encoding.

To anticipate my results, in contrast to MDMA at encoding in the previous chapter, which only impacted recollection, I show that alcohol and other $GABA_A$ PAMs at encoding strongly impact both recollection and familiarity, a finding that may speak to their ability to cause "blackouts." Second, I replicate previous findings that post-encoding $GABA_A$ PAMs can enhance episodic memory, an effect that has not been found with cannabis or other amnestic drugs. I also extend these consolidation effects by showing that they impact both recollection and

familiarity. Although this reanalysis did not find robust consolidation enhancements for emotional memories, I discuss potential reasons for why this may be.

## Background

It is well established that alcohol and other $GABA_A$ positive allosteric modulators (PAM) can have paradoxical effects on episodic memory. When these drugs are administered prior to encoding, they impair memory (e.g., Kamboj & Curran, 2006; Weafer, Gallo, & de Wit, 2016a), but when they are administered immediately post-encoding, they enhance memory for the recently encoded information (known as 'retrograde facilitation'; Mednick et al., 2013; Weafer et al., 2016a). To explain these opposing drug effects during different stages of memory, Wixted (2004) argued that $GABA_A$ PAMs disrupt the encoding of new information in the hippocampus (i.e., by disrupting new long-term potentiation or LTP), while at the same time sparing the hippocampally-based consolidation of previously encoded information (i.e., by sparing pre-drug LTP). If it is assumed that hippocampal processing of new information interferes with the consolidation of previously encoded information, then disrupting the former should remove this interference and improve memory for the latter. Additionally, some studies have shown that post-encoding $GABA_A$ PAMs can directly enhance sleep-based consolidation processes, and such enhancements are related to improvements in hippocampally-dependent memory (Mednick et al., 2013; Kaestner, Wixted, & Mednick, 2013; Niknazar, Krishnan, Bazhenov, & Mednick, 2015).

Although these effects of alcohol and other $GABA_A$ PAMs are well established, the impact of alcohol on different episodic memory processes is less clear. According to dual-process theories, episodic memories can be associated with either recollection or familiarity (Yonelinas, 2002). Recollection refers to a hippocampally-dependent retrieval of specific details

bound to an event or retrieval cue, whereas familiarity refers to a perirhinal-dependent memory signal defined as a 'feeling of knowing' that an event or test stimulus had occurred in the past without recollecting associated details. Prior work has suggested that $GABA_A$ PAMs administered at encoding selectively impair recollection with less consistent or no effects on familiarity (for discussion, see Yonelinas, 2002). This effect is consistent with the idea that $GABA_A$ can impair hippocampal processing, which would be expected to impair recollection more than familiarity. However, *N*-methyl-D-aspartate receptor antagonism, which directly impairs new hippocampal LTP while also maintaining pre-drug LTP (e.g., Villarreal, Do, Haddad, & Derrick, 2002), has been found to impair both recollection and familiarity when administered at encoding (Hetem, Danion, Diemunsch, & Brandt, 2000). Furthermore, modulation of $GABA_A$ receptors in perirhinal cortex can affect familiarity-based memory in an animal model (Kim et al., 2014), suggesting that systemic administration of $GABA_A$ PAMs might strongly impact both recollection and familiarity.

One reason that prior work administering $GABA_A$ PAMs during encoding failed to find robust familiarity impairments may be that these studies did not use sensitive measures of familiarity. As reviewed next, most of the studies in this area implemented recognition memory tests on which participants are asked if they recollect specific details of a test stimulus or instead if the stimulus is familiar without recollection (i.e., the remember/know procedure; Tulving, 1985). However, while a 'remember' response provides an estimate of recollection, it is thought that a 'know' response provides an underestimate of familiarity because these responses can only be made when recollection fails. According to some dual-process models, recollection and familiarity are independent and can sometimes co-occur so that a correction procedure is needed to effectively estimate familiarity from this procedure (the independence remember/know or IRK

procedure; Yonelinas, 2002). Prior work has not uniformly applied this correction to remember/know data, making null results of $GABA_A$ PAMs on familiarity difficult to interpret.

We searched the literature for studies in which $GABA_A$ PAMs were administered prior to encoding and used the remember/know procedure at retrieval, yielding 11 studies. In most of these studies the drug had minimal impact on or even increased uncorrected 'know' responses, leading to the conclusion that familiarity was relatively unaffected. However, we applied the IRK procedure to these studies, and a different picture emerged. As can be seen from Table 10, $GABA_A$ PAMs strongly reduced IRK familiarity estimates for studied items ($t(10) = 2.77$, $p = .020$, $d = .84$; paired, two-tailed, averaged across drugs/doses when multiple $GABA_A$ manipulations were used), as well as estimates of the accuracy of familiarity-based responding ($t(7) = 4.55$, $p = .003$, $d = 1.61$), sometimes in a dose-dependent manner.

| | *p*('old') | | *p*('R') | | *p*('K') | | IRK F | | Acc | R Acc | K Acc | IRK F Acc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hits | FAs | Hits | FAs | Hits | FAs | Hits | FAs | | | | |
| Curran et al. (1993) | | | | | | | | | | | | |
| PLA | .83 | .11 | .68 | .03 | .15 | .08 | .47 | .08 | .72 | .65 | .07 | .39 |
| LOR (2 mg) | .70 | .11 | .44 | .03 | .26 | .08 | .46 | .08 | .59 | .41 | .18 | .38 |
| Bishop & Curran (1995) | | | | | | | | | | | | |
| PLA | .95 | .05 | .52 | .00 | .43 | .05 | .90 | .05 | .90 | .52 | .38 | .85 |
| LOR (2 mg) | .87 | .12 | .34 | .01 | .54 | .11 | .82 | .11 | .75 | .33 | .43 | .71 |
| Curran & Hildebrandt (1999) | | | | | | | | | | | | |
| PLA | .65 | .03 | .43 | .01 | .28 | .07 | .50 | .07 | .61 | .42 | .21 | .43 |
| ALC (.28/.26 g/kg) | .45 | .02 | .26 | .01 | .26 | .03 | .34 | .03 | .43 | .25 | .22 | .31 |
| Milani & Curran (2000) | | | | | | | | | | | | |
| PLA | .74 | .03 | .51 | - | .23 | - | .47 | - | - | - | - | - |
| ALC (.28/.26 g/kg) | .72 | .02 | .51 | - | .21 | - | .43 | - | - | - | - | - |
| Mintzer & Griffiths (2000) | | | | | | | | | | | | |

**Table 10.** Effects of $GABA_A$ PAMs at encoding on the remember/know procedure across 11 studies. Independence remember/know familiarity estimates show that in most cases, drug-induced amnestic effects are numerically apparent for IRK F hits and/or IRK F accuracy (hits - false alarms). Blanks indicate that these data were not provided in the original study. Two doses of alcohol within a row indicate doses for males and females, respectively. All drugs can be assumed to be oral unless otherwise stated. See Methods for data reduction procedures and computations. PLA = placebo, LOR = lorazepam, ALC = alcohol, TRI = triazolam, DIA = diazepam, MID = midazolam, FA = false alarm, R = remember, K = know, IRK F = independence remember/know familiarity, Acc = accuracy.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PLA | .85 | .09 | .67 | .04 | .18 | .05 | .55 | .05 | .76 | .63 | .13 | .49 |
| TRI (.125 mg/70 kg) | .70 | .18 | .48 | .09 | .22 | .09 | .42 | .10 | .52 | .39 | .13 | .32 |
| TRI (.25 mg/70 kg) | .69 | .29 | .43 | .14 | .26 | .15 | .46 | .17 | .40 | .29 | .11 | .28 |
| Duka et al. (2001) | | | | | | | | | | | | |
| PLA | .34 | .07 | .23 | - | .11 | - | .14 | - | .27 | - | - | - |
| ALC (.8 g/kg) | .37 | .06 | .17 | - | .21 | - | .25 | - | .31 | - | - | - |
| Huron et al. (2001) | | | | | | | | | | | | |
| PLA | .85 | .08 | .62 | .01 | .23 | .07 | .61 | .07 | .77 | .61 | .16 | .53 |
| LOR (.038 mg/kg) | .81 | .22 | .49 | .03 | .32 | .19 | .63 | .20 | .59 | .46 | .13 | .43 |
| DIA (.3 mg/kg) | .73 | .09 | .40 | .01 | .34 | .09 | .57 | .09 | .64 | .39 | .25 | .48 |
| Huron et al. (2002) | | | | | | | | | | | | |
| PLA | .89 | .02 | .65 | .01 | .24 | .01 | .69 | .01 | .87 | .64 | .23 | .68 |
| LOR (.026 mg/kg) | .74 | .01 | .50 | .00 | .24 | .01 | .48 | .01 | .73 | .50 | .23 | .47 |
| LOR (038 mg/kg) | .61 | .02 | .33 | .01 | .28 | .01 | .42 | .01 | .59 | .32 | .27 | .41 |
| Hirshman et al. (2002) | | | | | | | | | | | | |
| PLA | .58 | .35 | .26 | .09 | .31 | .26 | .42 | .29 | .23 | .17 | .05 | .13 |
| MID (.03 mg/kg IV) | .40 | .32 | .15 | .12 | .25 | .20 | .29 | .23 | .08 | .03 | .05 | .07 |
| Bisby et al. (2010) | | | | | | | | | | | | |
| PLA | .72 | .03 | .46 | - | .35 | - | .65 | - | .69 | - | - | - |
| ALC (.4 g/kg) | .61 | .06 | .43 | - | .22 | - | .38 | - | .55 | - | - | - |
| ALC (.6 g/kg) | .55 | .02 | .35 | - | .29 | - | .45 | - | .53 | - | - | - |
| ALC (.8 g/kg) | .46 | .07 | .31 | - | .22 | - | .31 | - | .38 | - | - | - |
| Reder et al. (2013) | | | | | | | | | | | | |
| PLA | .44 | .11 | .23 | .04 | .21 | .07 | .27 | .08 | .33 | .20 | .13 | .19 |
| MID (.03 mg/kg IV) | .34 | .19 | .17 | .08 | .18 | .11 | .21 | .12 | .15 | .09 | .07 | .09 |

**Table 10** continued.

In contrast to these effects of $GABA_A$ PAMs at encoding, we are unaware of studies that have assessed the effects of post-encoding $GABA_A$ PAMs on the recollection and familiarity for previously encoded information. Studies using tasks thought to tap into recollection have found memory to be retroactively enhanced via $GABA_A$ PAMs during the consolidation window (e.g., Mednick et al., 2013; Weafer et al., 2016a), but it is unclear if such effects extend to familiarity. On the one hand, to the extent that the drug during encoding impairs processing that leads to familiarity, one also might expect that the drug during post-encoding consolidation will facilitate the familiarity of information encoded prior to the drug, analogous to the aforementioned drug effects on hippocampal memory. On the other hand, direct enhancement of consolidation processes via post-encoding $GABA_A$ PAMs appears to selectively facilitate performance on hippocampally-dependent memory tasks and not tasks less dependent on hippocampal processing, such as motor sequence and perceptual learning (Mednick et al., 2013). Therefore, this latter mechanism may not facilitate familiarity.

No prior study has investigated the impact of post-encoding alcohol on recollection and familiarity, but a recent study by Weafer et al. (2016a) collected data that are directly relevant to this issue. Weafer et al. tested the effects of alcohol on the encoding and consolidation of picture memories. Participants first encoded emotional and neutral pictures, and then on a later memory test they were given picture labels and attempted to recall whether the label had previously been associated with a picture, a procedure aimed at eliciting picture recollections. There were two key findings. The first was that alcohol administered prior to encoding disproportionately impaired memory for emotional over neutral pictures, consistent with other studies of $GABA_A$ PAMs during encoding (Brignell, Rosenthal, & Curran, 2007; Buchanan, Karafin, & Adolphs, 2003; Kamboj & Curran, 2006). The second was that post-encoding alcohol enhanced memory

but predominantly for neutral pictures. The prior literature is less clear on this particular effect. Previous post-encoding $GABA_A$ PAM studies have found equal retroactive enhancements of neutral and emotional information (Bruce & Pihl, 1997), retroactive enhancements of positive but not negative information (Bruce, Shestowsky, Mayerovitch, & Pihl, 1999), or greater retroactive enhancements of emotional compared to neutral information (Kaestner et al., 2013; Knowles & Duka, 2004). The reason for these discrepant findings is unclear, as there were several methodological differences between studies. We return to this topic in the General Discussion.

In the present study, we reanalyzed the confidence data from Weafer et al. (2016a) using a dual process signal detection (DPSD) analysis (Yonelinas, 2002) to estimate the effects that alcohol during the encoding and consolidation phases had on recollection and familiarity. Although Weafer et al. (2016a) used a cued memory task to target picture recollections, as we describe below, their methodology left open the possibility that familiarity also could have contributed, thereby opening the door to a dual-process analysis. By estimating recollection and familiarity from Weafer et al., we aimed to (1) see if the DPSD procedure converges with prior remember/know studies in showing both recollection and familiarity impairments via $GABA_A$ PAMs at encoding, (2) see if familiarity can be retroactively enhanced via $GABA_A$ PAMs at consolidation, and (3) see if this new analysis can uncover retrograde facilitation of emotional information.

## Methods

### Participants

This study is described in greater detail elsewhere (Weafer et al., 2016a). Fifty-nine healthy participants (21-30-years-old, 33 males) were recruited from the community through

online and printed advertisement. Exclusion criteria included current or past year Axis I DSM-IV disorder, lifetime substance dependence, >5 cigarettes per day, less than a high school education, lack of English fluency, a body mass index outside 19-26 $kg/m^2$, daily use of any medication other than birth control, pregnancy, lactating, or planning to become pregnant in the next 3 months. Participants were eligible if they reported consuming an average of 10-30 standard drinks per week with at least 1 heavy drinking episode (4 or 5 drinks per occasion for men and women, respectively) in the last month. A standard drink was defined as a 12 oz can or bottle of beer, a 5 oz glass of wine, a 1.5 oz shot of distilled spirits, or a mixed drink with 1.5 oz of distilled spirits. These minimum drinking criteria were to ensure that participants could tolerate the dose of alcohol. Women not taking hormonal contraceptives were tested during their follicular phase because hormonal fluctuations can influence responses to drugs (White, Justice, & de Wit, 2002).

Qualifying participants attended an orientation session to sign a consent form and practice tasks. In order to minimize expectancy, participants were informed that they could receive a stimulant, sedative, alcohol, or placebo. Participants were instructed to consume their normal amounts of caffeine and nicotine before sessions but to abstain from using drugs, including alcohol, for 24 hours prior to each session. Participants were notified that there would be drug tests and that they would be rescheduled if they tested positive for any recent drug use. Participants were not to eat after 9:00 AM on study days. Following completion of the study, participants were fully debriefed and monetarily compensated. The study took place at the University of Chicago Medical Center and was approved by the Institutional Review Board.

**Drug**

Alcohol (.8 g/kg for men and .7 g/kg for women) and placebo were administered in black cherry sugar-free gelatin for fast consumption and to mask the taste. These doses were chosen to produce peak blood alcohol concentrations (BAC) of 80 mg/100 ml. Alcohol gelatin consisted of 3 parts 95% alcohol and 5 parts water, and placebo gelatin consisted of 8 parts water. Participants consumed individual servings (5 g alcohol each) in black 2 oz cups. Number of servings ranged from 10 to 14 for men and 7 to 10 for women. Participants received the same number of servings for both alcohol and placebo gelatin.

**Design**

This study used a two-session design in which the first session was for encoding stimuli, and the second session, 48 hours later, was a retrieval session for testing memory. Subjects were randomly assigned to one of three groups, one that received alcohol just prior to encoding and placebo immediately post-encoding during the consolidation window (Encoding, $N = 20$, 11 males), one that received placebo during encoding and alcohol during consolidation (Consolidation, $N = 20$, 11 males), and one that received placebo at both time points (Placebo, $N = 19$, 11 males). Besides the drug manipulation, the procedure for all groups was identical and double-blinded. All sessions began at 1:00 PM.

**Stimuli**

Stimuli consisted of 144 images from the International Affective Picture Set (IAPS; Lang, Bradley, & Cuthbert, 2008) and 2-3 word labels (e.g., 'angry man face,' 'sailboat on ocean') describing these images, as well as 96 alcohol-related and non-alcoholic beverage-related images, data for which will not be reported here (see Weafer, Gallo, & de Wit, 2016b). The images included emotionally negative, neutral, and positive pictures and had the following

mean normed valences and arousals, respectively: negative 2.95 and 5.66, neutral 5.31 and 3.71, positive 7.17 and 5.58. These pictures were split into two comparable sets for counterbalancing studied and nonstudied items across participants.

**Procedure**

On the morning of experimental sessions, participants first completed compliance measures including BAC (Alco-sensor III, Intoximeters, St. Louis, MO), a urine drug test (ToxCup, Branan Medical Co. Irvine, CA), and a pregnancy test (females only; Aimstrip, Craig Medical, Vista, CA), as well as baseline cardiovascular and mood measures. Participants then consumed the first serving of gelatin within 5 minutes, and 20 minutes later, participants viewed all 144 labels in random order, half of which were followed by the corresponding picture. For each label, participants rated on a five-point scale how much they would like to see the corresponding picture. When a picture was presented, participants rated its positivity and negativity on a 5 × 5 grid with positivity and negativity on orthogonal axes and its arousal on a 5-point scale. This phase was self-paced.

After encoding stimuli, participants consumed the second serving of gelatin and stayed in the lab for another 3.5 hours. For the first two hours, they listened to music provided to them, but they were not allowed to watch movies, use the Internet, read, or sleep. Afterward, they were allowed to read or watch movies for the remainder of the session and when their BAC had fallen below 40 mg/100 ml.

During the retrieval session, participants were given two surprise memory tests, a cued recollection test and a picture recognition test. For the cued recollection test, participants were presented with each label in random order and asked whether they had seen the corresponding picture (yes/no). Afterward, they rated their confidence on a five-point scale. Immediately after

the cued recollection test was a picture recognition test in which participants were presented with pictures they had seen as well as the pictures for the labels that were not presented with pictures. They were again to decide if they had seen each picture and make a confidence rating.

**Dependent Measures**

Several dependent measures were acquired in Weafer et al. (2016a), but for the purpose of this reanalysis, we focused on estimates of recollection and familiarity from the confidence data in the cued recollection phase. The recognition memory task was confounded with the prior cued recollection task in that study, and was argued to be less sensitive to drug effects by Weafer et al. (2016a). Moreover, because distributions of recollection estimates from the recognition phase were not normally distributed (see Statistical Analysis below), these data will not be discussed.

In order to dissociate the contributions of recollection and familiarity in the cued recollection phase, confidence data were submitted to a DPSD analysis using the ROC Toolbox for MATLAB (Koen, Barrett, Harlow, & Yonelinas, 2016). Confidence data were first combined between 'yes' and 'no' responses to create a 10-point scale (confidence data from 'no' responses were reverse scored). The cumulative proportion of hits is plotted against the cumulative proportion of false alarms starting with the most stringent criterion (i.e., proportion of hits and false alarms given the highest level of confidence) to the most liberal criterion with the final point at (1,1) when the cumulative proportion of hits and false alarms is equal to 1. A receiver operator characteristic (ROC) curve is then fit to these points using maximum likelihood estimation, but unlike typical ROC curves, which begin at (0,0), the DPSD model assumes a threshold process (recollection) can take place on some proportion of trials that is reflected by the *y*-intercept of the ROC curve (measured as a probability). In contrast, familiarity is thought to

be a signal detection process, reflected in the curvilinearity of the function (measured in *z* score units).

**Statistical Analysis**

Encoding and Consolidation groups were compared separately to the Placebo group. Estimates of recollection and familiarity derived from ROC curves are typically calculated individually for each participant (e.g., Koen, Aly, Wang, & Yonelinas, 2013). However, because the number of targets and lures per valence condition was low (i.e., 24 targets and 24 lures), confidence data were collapsed across participants to generate aggregate ROC curves with 480 hits and 480 false alarms per valence condition in the Encoding and Consolidation groups and 456 hits and 456 false alarms per valence condition in the Placebo group (i.e., 9 ROC curves in total). Parameter reliability was then assessed via a non-parametric bootstrapping procedure. For each condition, distributions of recollection and familiarity estimates were generated by randomly sampling *N* subjects with replacement (i.e., 20 for Encoding and Consolidation and 19 for Placebo) and running an ROC analysis on each iteration (10,000 iterations). Pairwise comparisons were then made by subtracting distributions and calculating the proportion of the difference distribution that is above 0. Confidence intervals for the difference of two means were obtained from the 2.5% and 97.5% quantiles of the difference distributions.

**Data Reduction and Computations for Table 10**

In order to organize the data from Table 10 in a fashion that makes it possible to compare the effects of $GABA_A$ agonists on familiarity across studies, certain procedures were taken. In Curran, Gardiner, Java, & Allen (1993), memory was tested at one, three, and five hours post-drug administration. Therefore, hit rates were averaged across time points. In Bishop and Curran (1995), hit and false alarm rates were averaged across physical level-of-processing and test

format conditions. Hit rates in generate and read conditions were averaged from Curran and Hildebrandt (1999) and Bisby, Leitz, Morgan, and Curran (2010). In Duka, Weissenborn, and Dienes (2001), a drug was administered at both encoding and retrieval. Only placebo-placebo (placebo at encoding, placebo at retrieval) and alcohol-placebo (alcohol at encoding, placebo at retrieval) conditions are reported for the explicit memory task. Furthermore, high and low association conditions were averaged. In Hirshman et al. (2002), hit rates were averaged across frequency and duration conditions, and false alarm rates were averaged across frequency conditions. In Reder et al. (2013), hit rates were averaged across fame, fan, and context reinstatement conditions, and false alarm rates were averaged across fame and fan conditions. When guess rates were included (Bisby et al., 2010; Bishop & Curran, 1995; Curran & Hildebrandt, 1999; Duka et al., 2001; Huron, Giersch, & Danion, 2002; Huron, Servais, & Danion, 2001), these were added to "know" rates, as guessing that an item is old likely relies on a weak familiarity signal. Even when guess rates were not combined with "know" responses, independence remember/know (IRK) familiarity estimates did not drastically differ. Finally, when the Deese-Roediger-McDermott task (for review, see Gallo, 2010) was used (Huron et al., 2001; Milani & Curran, 2000; Mintzer & Griffiths, 2000), only hits and false alarms to unrelated lures (when available) were reported.

Because a "know" response is the probability of familiarity in the absence of recollection, IRK familiarity estimates can be computed to avoid underestimation (Yonelinas, 2002). IRK familiarity estimates are measured by dividing $p$("know") by 1 - $p$("remember) for both hit and false alarm rates.

# Results

## Placebo vs. Encoding

The distributions of DPSD-based recollection and familiarity estimates from the bootstrapping procedure were all normal (Figures 7 and 8). Negative (95% CI: [.17, .39], $p <$ .001), neutral (95% CI: [.07, .27], $p < .001$), and positive (95% CI: [.10, .32], $p < .001$) recollection estimates in the Encoding group were reduced compared to the Placebo group. The Encoding and Placebo groups also differed in their negative (95% CI: [.18, .76], $p < .001$), neutral (95% CI: [-.01, .50], $p = .032$), and positive (95% CI: [.05, .62], $p = .012$) familiarity estimates, though the confidence interval for neutral familiarity estimates suggests a less reliable effect. These findings show that alcohol at encoding can impair both recollection and familiarity, and consistent with Weafer et al. (2016a), these effects seem to be larger for emotional than neutral items.

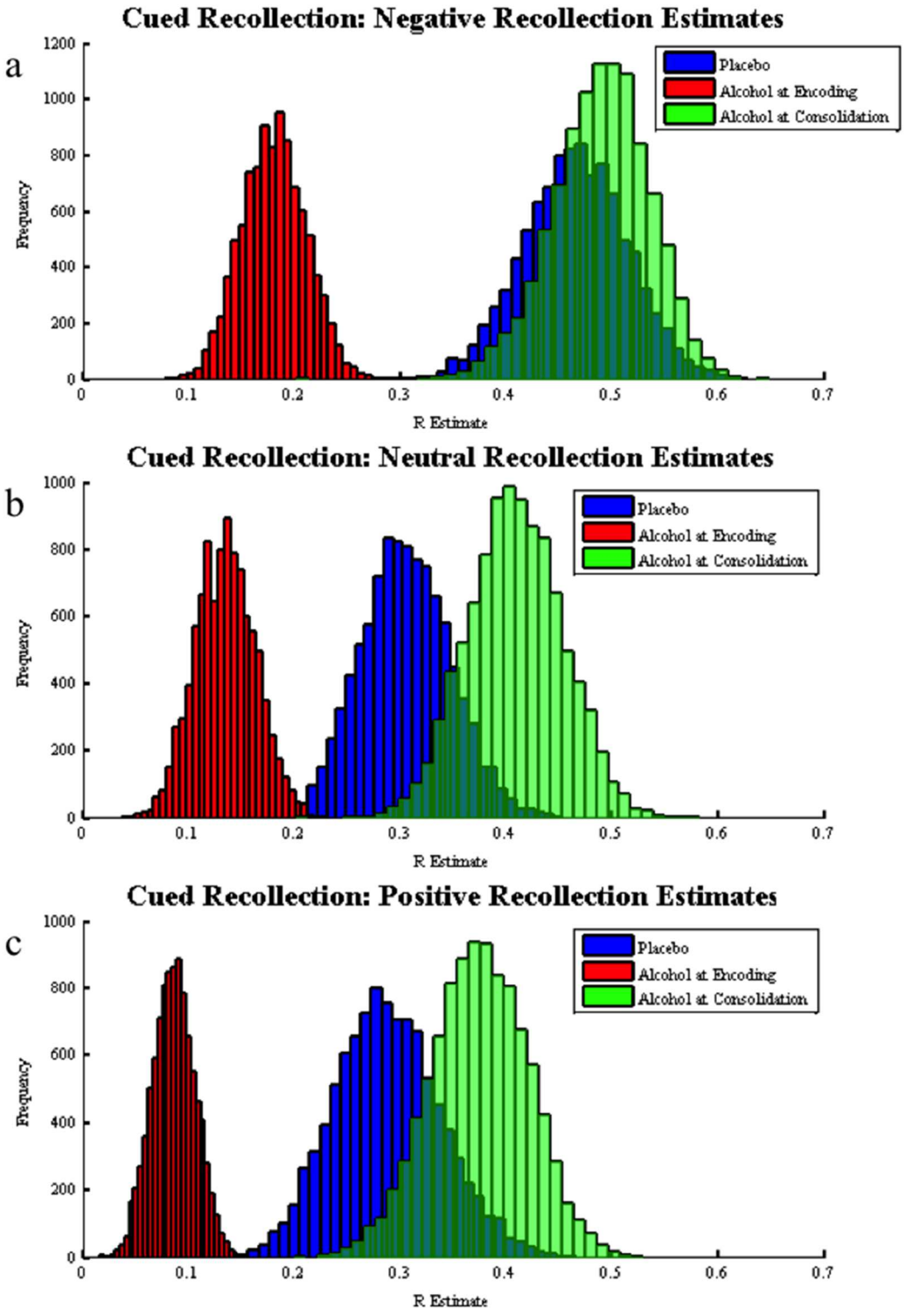


**Figure 7.** Distributions of **a.** negative, **b.** neutral, and **c.** positive dual process signal detection-based recollection estimates generated from the bootstrapping procedure on the cued recollection confidence data in Chapter 4.

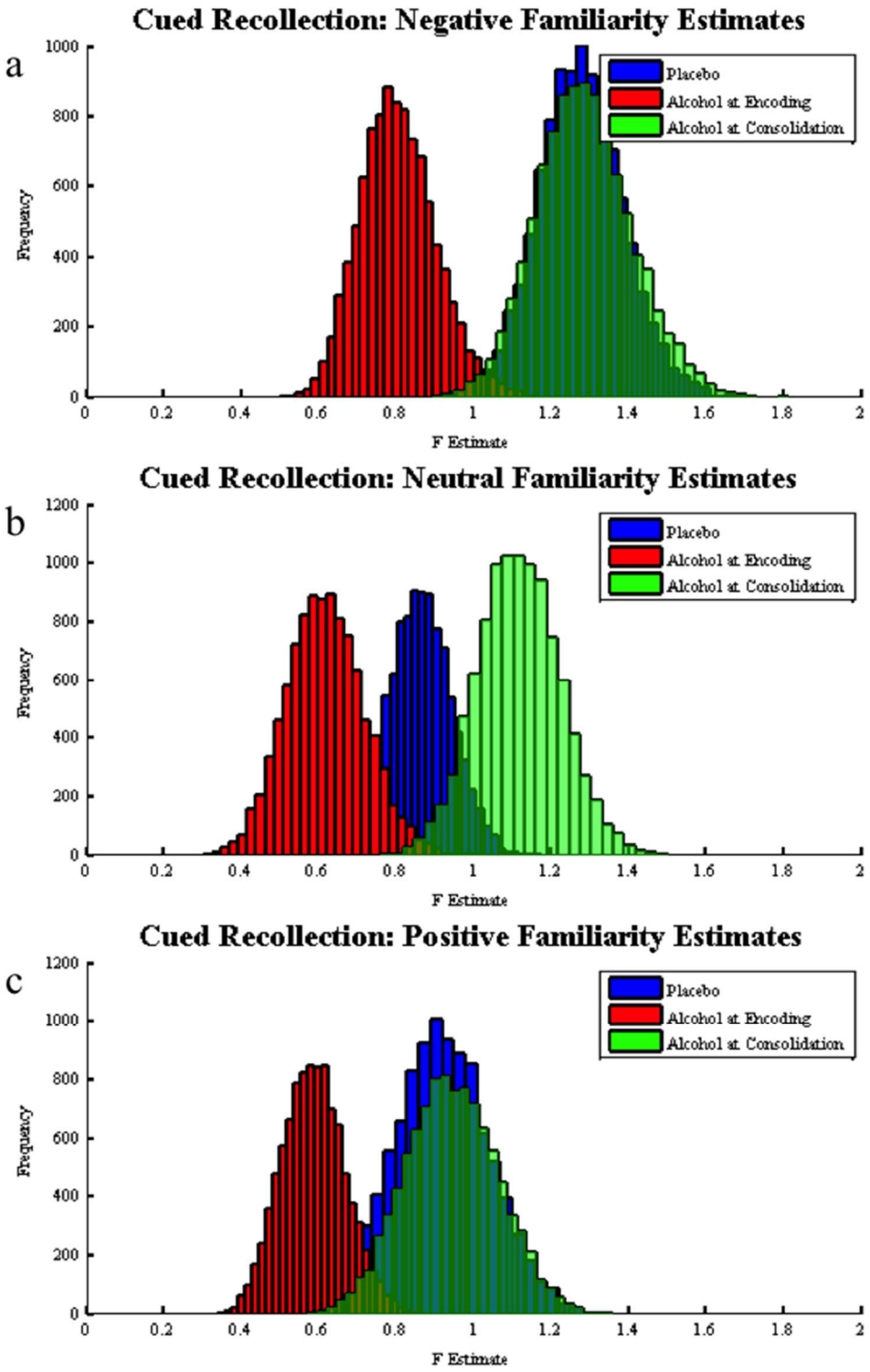


**Figure 8.** Distributions of **a.** negative, **b.** neutral, and **c.** positive dual process signal detection-based familiarity estimates generated from the bootstrapping procedure on the cued recollection confidence data in Chapter 4.

**Placebo vs. Consolidation**

Compared to the Placebo group, we found that alcohol during Consolidation increased both recollection (95% CI: [-.02, .22], $p = .048$) and familiarity (95% CI: [-.01, .52], $p = .028$) estimates for neutral information (Figures 7b and 8b). This shows that the boost for neutral items reported by Weafer et al. (2016a) was due to increases in both recollection and familiarity. By contrast, neither negative (95% CI: [-.31, .34], $p > .250$) nor positive (95% CI: [-.31, .35], $p > .250$) familiarity estimates were impacted by post-encoding alcohol. Whereas Weafer et al. did not observe a significant effect of alcohol during consolidation on overall memory accuracy for emotional items, with this new analysis we found a statistical trend that positive recollection estimates were greater in the Consolidation group (Figure 7c; 95% CI: [-.05, .22], $p = .107$). In contrast, recollection was not impacted for negative items (95% CI: [-.11, .15], $p > .250$). These effects are consistent with a prior study that found retrograde facilitation effects of alcohol for positive but not negative material (Bruce et al., 1999). Supporting this trend, when negative and positive recollection estimates were directly compared, the better recollection memory for negative compared to positive items appeared to be attenuated in the Consolidation group (Placebo: 95% CI: [.08, .27], $p < .001$; Consolidation: 95% CI: [.03, .20], $p = .004$).

## Discussion

In this paper we report a reanalysis of data in Weafer et al. (2016a), revealing that alcohol during the encoding phase or the post-encoding consolidation phase can impact both recollection and familiarity. Whereas our findings for recollection estimates are broadly consistent with prior work showing that alcohol at encoding can dampen recollection (Table 10) and alcohol post-encoding can retroactively enhance performance on tasks thought to tap into recollection (Mednick et al., 2013; Weafer et al., 2016a), the finding that similar effects apply to familiarity is

novel. Prior work testing the effects of $GABA_A$ PAMs on encoding has emphasized recollection more than familiarity effects, but application of the IRK procedure to familiarity-based responses (Table 10) demonstrates familiarity impairments in line with those observed here. Moreover, this reanalysis provides the first demonstration that familiarity can be retroactively enhanced via post-encoding $GABA_A$ stimulation.

These encoding effects are consistent with a study that found midazolam at encoding to attenuate the neural correlates of both recollection and familiarity (Nyhus & Curran, 2011). Like familiarity, aspects of conceptual priming (Wang, Ranganath, & Yonelinas, 2014) and semantic memory (Davies et al., 2004) are thought to rely on perirhinal cortex, so one mechanism by which alcohol may reduce familiarity is through attenuating semantic or implicit memory processes that are thought to support feelings of familiarity (Yonelinas, 2002). Although $GABA_A$ PAMs do not typically affect implicit or semantic memory (for review, see Curran, 1999), there are some cases in which they can (e.g., Hirshman, Passannante, & Henzler, 1999; Stewart et al., 1996; Boucart et al., 2002).

The retrograde facilitation of familiarity that we found in this reanalysis may rely on different mechanisms than retrograde facilitation of recollection. Whereas retrograde facilitation of recollection is thought to be due to preventing retroactive interference in the hippocampus (Wixted, 2004), retrograde facilitation of familiarity may be due to preventing retroactive interference in perirhinal cortex. Retrograde facilitation of recollection might also be supported by $GABA_A$ modulation of sleep-based consolidation processes, such as prolonging slow-wave sleep (e.g., Ebrahim et al., 2013; Mednick et al., 2013 and accompanying hippocampal replay that are associated with recollection (Rasch & Born, 2008). Because our design used a 48-hour delay between the encoding and retrieval phases, it is possible that alcohol affected sleep-based

consolidation processes during the first night, especially given that alcohol can impact sleep many hours after consumption (Ebrahim et al., 2013).

This reanalysis also found that post-encoding alcohol significantly enhanced neutral estimates of recollection and had a similar (albeit nonsignificant) effect on positive estimates of recollection, but there was no effect on negative estimates of recollection. This pattern is consistent with one study that found positive but not negative memory to be retroactively enhanced when a 24-hour delay was implemented between encoding and retrieval (Bruce et al., 1999). However, other studies have found the opposite effect, indicating more selective retrograde facilitation of negative compared to neutral information (Kaestner et al., 2013; Knowles & Duka, 2004). An important methodological difference between these studies is that the former studies introduced a long delay between the encoding and retrieval phases, whereas the latter studies did not. This pattern suggests that the retrograde facilitation effects of alcohol may interact with emotional memory consolidation processes that occur over longer delays. For example, although $GABA_A$ PAMs may enhance certain sleep-based consolidation processes (Kaestner et al., 2013; Mednick et al., 2013; Niknazar et al., 2015), they may degrade rapid eye movement sleep (e.g., Ebrahim, Shapiro, Williams, & Fenwick, 2013; Kaestner et al., 2013), a stage of sleep that may be particularly important for emotional memory processing (Groch, Wilhelm, Diekelmann, & Born, 2013; Wagner, Gais, & Born, 2001). Another possibility is that the replay of negative memories during sleep requires coordinated reactivations between the hippocampus and amygdala (Girardeau, Inema, & Buzsáki, 2017), but this may be attenuated by $GABA_A$ PAMs' disruption of amygdalar activity during the processing of negative emotional information (Del-Ben et al., 2010; Gilman et al., 2008; Paulus et al., 2005). Our study was not

designed to test between these possibilities, and additional work is needed to understand why negative memories may be more resistant to retrograde facilitation effects than other memories.

In conclusion, we found that alcohol impaired both recollection and familiarity of emotional and neutral information during encoding and enhanced both recollection and familiarity of neutral information during consolidation. Related to the encoding findings, it has been shown that lorazepam at encoding can reduce both gist and detail of emotional and neutral memory (Kamboj & Curran, 2006). Such global impairments on encoding speak to anecdotes of 'blacking out' from $GABA_A$ PAMs in spite of the occurrence of an emotional event. Such experiences are typically described as a complete memory loss rather than partial recollections (i.e., 'browning out') or familiarity with the event upon its description. This more global memory impairment could explain why alcohol and other $GABA_A$ PAMs are used as so-called 'date rape' drugs, but other amnestic drugs like ±3,4-methylendioxymethamphetamine, which appear to impact recollection but not necessarily familiarity at recreational doses (Doss, Weafer, Gallo, & de Wit, 2017), are not typically used for such a purpose. Collectively, these studies highlight the importance of differentiating drug effects on recollection and familiarity, as well as how administration of the drug during different stages of episodic memory can impact these processes.

# General Discussion

This dissertation explored how psychoactive drugs can differentially impact the encoding, consolidation, and retrieval of emotional episodic memories. In Chapter 1, I identified consistencies in the literature regarding drug effects at each of these phases on emotional episodic memories. When the effects of most drugs are isolated to memory encoding, emotional memory, both negative and positive, is more strongly impacted compared to neutral memory. Few pharmacological studies of emotional memory have isolated drug effects to the consolidation phase, but one trend seems to be that the emotional selectivity of retrograde facilitation via $GABA_A$ PAMs depends on the delay between encoding and retrieval. That is, shorter delays appear to more selectively enhance emotional memory, and longer delays more selectively enhance neutral memories. Finally, drug effects isolated to memory retrieval drive false memories, perhaps with some specificity for positive memories. Together, these findings demonstrate the importance of isolating drug effects to different phases of episodic memory.

In Chapters 2 and 3, I found that when the effects of THC and MDMA are isolated to memory retrieval, false memories increase. Although there was some evidence that MDMA also suppressed emotional memory retrieval for studied events, the memory impairments observed in previous work were most likely due to THC and MDMA's effects on encoding. Previous work could not differentiate encoding and retrieval effects because drugs were administered prior to encoding and memory was tested soon after while drug effects persisted through memory retrieval. In contrast, by implementing a delay between encoding and retrieval and administering drugs prior to only one of the phases, I was able to definitively isolate these distinct effects on encoding and retrieval.

Another important finding of this dissertation was that MDMA at encoding, like other drugs, has a stronger impact on emotionally negative and positive material. That is, in Chapter 3, MDMA administered prior to encoding was found to have a stronger amnestic effect on negative and positive material. This effect was revealed when process dissociation procedures were implemented to estimate drug effects on recollection and familiarity, with only the former impacted by MDMA. This same analysis also found emotionally selective impairments of alcohol on encoding in Chapter 4. Interestingly, one previous study that did not isolate the effects of alcohol to encoding (i.e., by testing memory immediately after encoding) found alcohol to impair emotional and neutral memory equally (Knowles & Duka, 2004), again highlighting the importance of utilizing delay periods to isolate drug effects.

Finally, by dissociating recollection and familiarity I also found qualitative differences between the effects of MDMA and alcohol on encoding. MDMA impaired recollection but not familiarity, whereas alcohol modulated both recollection and familiarity. These differential effects on component processes, together with their shared emotional specificity, may speak to their utility in medicine. For example, MDMA may be better posited as an adjunct to psychotherapy to facilitate changes in maladaptive memories upon their retrieval. The selective impact on memory encoding may also permit new learning while diminishing the encoding of strong, emotional recollections. On the other hand, the more global impact of $GABA_A$ PAMs may be more appropriate for precluding the encoding of highly negative events during flashbacks or panic attacks. Below I suggest considerations for future work testing the effects of drugs on emotional episodic memories that may be informative to both basic science and clinical research.

## Component Processes

Because emotion does not typically enhance all aspects of episodic memory, it is worth teasing apart the component processes affected by drugs. For example, emotion is known to more selectively impact item recollections as opposed to context recollections or familiarity (Yonelinas & Ritchey, 2015). Whereas recollection is the hippocampally-dependent retrieval of specific details and associations, familiarity is a cortically-dependent feeling of knowing that an event has happened in the absence of contextual details (Yonelinas, 2002). It has been suggested that familiarity is only weakly impacted or not impacted at all by $GABA_A$ PAMs at encoding (for discussion, see Yonelinas, 2002). However, in my reanalyses in Chapter 4, I found that familiarity is indeed strongly diminished by $GABA_A$ PAMs at encoding (Doss et al., submitted). Similarly, both recollection and familiarity were retroactively enhanced when alcohol was administered immediately post-encoding. This makes sense given the widespread distribution of $GABA_A$ receptors, as well as reports of "blacking out" from $GABA_A$ PAMs. Similarly, lorazepam has been found to impair both gist and detail memory (Kamboj & Curran, 2006), though a study with triazolam found only deficits in gist memory (Buchanan et al., 2003). Although we have highlighted similarities among $GABA_A$ PAMs throughout this review, this discrepancy may speak to potential differences, with lorazepam being a special case of a benzodiazepine that can impact both explicit and implicit memory processes (for discussion, see Curran, 1999).

Our studies also suggest that various drugs at retrieval drive false recollections rather than false memories based on familiarity or changes in response bias. In Ballard et al. (2014), amphetamine at retrieval increased the recall of details for nonstudied pictures in the absence in any kind of cue. In Doss et al. (2018), MDMA was found to increase high confidence false

alarms for pictures that were cued with labels. That is, participants were able to form a detailed mental image that they misattributed to having been actually studied. THC was also found to drive high confidence false recollections for pictures cued by labels, as well as subjective false recollections for details (i.e., "remember" responses; Doss et al., in review). This latter finding on subjective recollections was also trending in the reanalysis of $GABA_A$ PAM studies in which drug effects persisted through both encoding and retrieval (Doss et al., submitted). Lastly, the ventral striatum, which I propose to underlie these memory distortions, has been specifically associated with recollection but not familiarity (King et al., 2017).

Few other psychopharmacological studies have attempted to dissociate recollection and familiarity. Ketamine appears to affect both recollection and familiarity (Hetem, Danion, Diemunsch, & Brandt, 2000), though lower doses may only impact recollection (Honey et al., 2005). Similar to $GABA_A$ PAMs and their ability to cause "blackouts," this impairment of both recollection and familiarity speaks to the widespread distribution of NMDA receptors and the idiosyncratic amnestic state produced by ketamine at higher doses (i.e., the "K-hole"; Muetzelfeldt et al., 2008). Scopolamine, another drug that can produce a densely amnestic state and has been used in kidnappings, impairs both recollection and familiarity (Sherman et al., 2003) and both gist and detail memory (Kamboj & Curran, 2006) when administered at encoding.

In contrast to these drugs, moderate doses of MDMA impact recollection but seem to leave familiarity unaffected (Doss et al., 2018). Furthermore, only specific measures of recollection were impacted that displayed the emotionally selective effects discussed in Chapter 1. I argue that this finding suggests that qualitative aspects of recollections might have been altered rather than complete failures to recollect. Different aspects of recollection (i.e., precision,

vividness, amount of qualitatively different details) have been a recent area of interest (e.g., Harlow & Yonelinas, 2016; Scimeca, McDonough, & Gallo, 2011), with potentially distinct neural underpinnings (Richter, Cooper, Bays, & Simons, 2016), and future work will have to disentangle how various drugs impact them.

## Clinical Significance and Future Directions

Although one focus of this review has been on the emotional episodic memories that are not remembered from amnestic drug manipulations at encoding, emotional memories that survive these manipulations may too be important to study with implications for addiction. Drugs are known to increase ventral striatal dopaminergic transmission either directly or indirectly (Yager et al., 2015). Ventral striatal activity may especially be heightened when drugs impoverish encoding, as the ventral striatum can compensate for the hippocampus under poor encoding conditions (Foerde, Knowlton, & Poldrack, 2006). Moreover, such striatal compensations can be accompanied by amygdalar activation (Antonova et al., 2011). However, if normal amygdalar activations during the encoding of emotional stimuli have been dampened by a drug (cf. Bedi, Phan, Angstadt, & de Wit, 2009; Del-Ben et al., 2010; Gilman et al., 2008; Paulus et al., 2005; Phan et al., 2008), it might be expected that ventral striatal compensation would be particularly strong.

Because negative emotional memories are especially thought to recapitulate encoding-related activity (Bowen et al., 2017), another prediction is that the sober retrieval of negative emotional memories that survived amnestic drug manipulations should result in greater ventral striatal activity. Such ventral striatal activity in the absence of drug effects may help elucidate how the retrieval of negative memories can support drug-seeking behavior. Furthermore, drugs that enhance encoding (e.g., dextroamphetamine) may too produce episodic memories that

strongly recapitulate ventral striatal activity, as these drugs directly impact the ventral striatum via dopaminergic modulation. Future work on the neural correlates of these emotional episodic drug memories may help outline the path of drug use to abuse (cf. Müller, 2013).

Another important insight that may come from emotional memory research will be how a single use of a drug can have long-lasting, potentially beneficial effects. Various drugs with purported rapid antidepressant action (e.g., ketamine, Sanacora et al., 2017; scopolamine, Jaffe, Novakovic, & Peselow, 2013; psychedelics, Carhart-Harris & Goodwin, 2017) may alter amygdalar responses to emotional stimuli after drug effects have dissipated (Roseman et al., 2017; Szczepanik et al., 2016). Of clinical relevance would be identifying whether such alterations impact emotional episodic memories. Antidepressant drugs, for example, not only alter emotional processing but also increase memory for positive compared to negative stimuli (Harmer, Goodwin, & Cowen, 2013). Therefore, it might be expected that rapid antidepressant action of certain drugs may also result in enhanced encoding, consolidation, or retrieval of positive memories.

Interestingly, the drug with the most evidence for rapid antidepressant action, ketamine, was found to most strongly impair positive memory encoding (Becker et al., 2017), suggesting that there could be a rebound effect on the encoding of positive memories that happens once the acute effects have subsided. A similar rebound effect is seen with the psychedelic psilocybin, which acutely attenuates amygdalar activations to negative emotional faces (Kraehenmann et al., 2015) but potentially increases these activations one day after psilocybin treatment (Roseman et al., 2017). It will be important in future work to explore whether these potential antidepressant effects occur after taking other psychoactive drugs to ensure that they truly are related to an

antidepressant effect rather than a common effect to all psychoactive drugs that may actually support abuse.

One of the most exciting clinical applications of memory research and pharmacology comes from studies of reconsolidation (Lee, Nader, & Schiller, 2017). In these studies, a reactivation phase exists between encoding and retrieval in which memories are cued in the context of a pharmacological or behavioral manipulation that is meant to strengthen, weaken, or distort these memories. The amnestic beta-adrenergic antagonist propranolol has been administered during this reactivation phase in several different reconsolidation paradigms sometimes producing selective impairments for emotional memories (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013). Reconsolidation paradigms may be of particular relevance to drugs that are being explored for their treatment of disorders such as PTSD and addiction (cf. Feduccia & Mithoefer, 2018), but parceling out drug effects on emotional memory encoding, consolidation, and retrieval would be important first steps.

Throughout this dissertation I have argued that it is critically important to disentangle the basic effects of various classes of drugs on the different phases of emotional episodic memories. My work has shown differential effects of drugs on encoding, consolidation, and retrieval, with different implications for clinical uses and addiction. However, this is just the start, as many drugs have yet to be tested on all phases of emotional episodic memory (e.g., consolidation), some drugs have never been tested on emotional episodic memory (e.g., psychedelics), and neuroimaging research in this area is scarce. Finally, although beyond the scope of this dissertation, how emotion interacts with state-dependent memory (i.e., drugs administered at encoding and retrieval) may be especially relevant for addiction. I believe that rigorous emotional episodic memory research with drug manipulations will lead to improvements in our

understanding of psychoactive drugs so that we can maximize potential benefits while reducing harms.

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