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Alcohol and Pharmacologically Similar Sedatives Impair Encoding and Facilitate Consolidation of both Recollection and Familiarity in Episodic Memory

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Abstract

Alcohol and other pharmacologically similar sedatives (i.e., GABA_A positive allosteric modulators or PAMs) impair the encoding of new episodic memories but retroactively facilitate the consolidation of recently encoded memories. These effects are consistent for recollection (i.e., the retrieval of details) but some mixed results have been reported for familiarity (i.e., a feeling of knowing a stimulus was presented). Here, with dual-process models, we reanalyzed prior work testing the effects of GABA_A PAMs at encoding or consolidation. Contrary to previous conclusions, we show that GABA_A PAMs at encoding consistently impair both recollection and familiarity when an independence correction is applied to familiarity-based responses. These findings were further confirmed and extended in a dual-process signal detection analysis of a recent study on the effects of alcohol during encoding or consolidation: Alcohol at encoding impaired both recollection and familiarity, whereas alcohol at consolidation enhanced both recollection and familiarity. These findings speak to the ability of alcohol and other GABA_A PAMs to induce ‘blackouts,’ highlighting the importance of dual-process approaches when analyzing drug manipulations at different phases of episodic memory.

Keywords

alcohol; GABA_A; episodic memory; recollection; familiarity; retrograde facilitation

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Disclosure of Interest

MKD, JW, NAR, and DAG report no conflict of interest.

Introduction

It is well established that alcohol and other GABA_A positive allosteric modulators (PAMs; i.e., sedating drugs such as benzodiazepines and hypnotics that facilitate activity at the GABA_A receptor) can have paradoxical effects on episodic memory. When administered prior to encoding, these drugs impair memory for the to-be-remembered information (e.g., Kamboj & Curran, 2006; Weafer, Gallo, & de Wit, 2016a), but when they are administered immediately post-encoding, they enhance memory for this same 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 preventing new long-term potentiation or LTP) while at the same time sparing the hippocampally-based consolidation of previously encoded information (i.e., by sparing the stabilization of 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.

Although these impairing and enhancing effects of alcohol and other GABA_A PAMs are well established, it is less clear how these drugs affect two key processes involved in episodic memory, recollection and familiarity. According to dual-process theories, episodic memories can be retrieved on the basis of recollection and familiarity (Yonelinas, 2002). Recollection refers to the retrieval of specific details bound to an event or retrieval cue, whereas familiarity refers to 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 no effects or even enhancements on familiarity (for discussion, see Yonelinas, 2002). This effect is consistent with the idea that GABA_A PAMs can impair the processing of new information in the hippocampus, given that recollection has been more strongly associated with hippocampal processing than familiarity (Yonelinas, Aly, Wang, & Koen, 2010). Understanding the differential impact of GABA_A PAMs, as well as other psychoactive drugs, on specific episodic memory processes may explain the underlying mechanisms of phenomena like ‘blacking out’ and aid in the development of pharmacological tools that selectively target abnormalities in memory disorders.

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. 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). Although a ‘remember’ response provides an estimate of recollection, a ‘know’ response is thought to underestimate 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 (the independence remember/know or IRK procedure; Yonelinas, 2002). Prior work (i.e., all studies in Table 1) has not applied this correction to

remember/know data, making null results of GABA_A PAMs on familiarity difficult to interpret.

In contrast to these effects of alcohol and other GABA_A PAMs at encoding, we are unaware of studies that have assessed the effects of post-encoding alcohol or other GABA_A PAMs on the recollection and familiarity for previously encoded information. Considering Wixted's account that retrograde facilitation involves preventing retroactive interference in the hippocampus, post-encoding GABA_A PAMs should enhance hippocampally-dependent recollection. This account is also consistent with past work that has used tasks thought to tap into recollection (e.g., Mednick et al., 2013; Weafer et al., 2016a). Nevertheless, it is less clear if or how familiarity would be impacted.

The Current Study

In the current paper we report two reanalyses addressing two unresolved questions: (1) How do pre-encoding alcohol and other GABA_A PAMs impact recollection and familiarity? (2) How do post-encoding alcohol and other GABA_A PAMs impact recollection and familiarity? To address the first question, we reanalyzed the remember/know results from experiments that administered GABA_A PAMs (including alcohol and benzodiazepines) prior to encoding using the IRK correction. We are unaware of any prior studies that administered alcohol or other GABA_A PAMs post-encoding with the remember/know procedure used at retrieval. However, the dual-process signal detection (DPSD) model is another method of estimating recollection and familiarity from confidence data (Yonelinas, 2002). Therefore, to address the second question, we conducted a DPSD analysis on the confidence data from a recent study that examined the impact of either pre- or post-encoding alcohol on emotional and neutral memory (Weafer et al. 2016a).

Study 1: Quantitative IRK Reanalysis of Prior Studies

For this analysis, we estimated the effects of alcohol and other GABA_A PAMs during the encoding phase on recollection and familiarity from published data. We identified 11 studies with GABA_A PAM manipulations during encoding and the remember/know procedure during retrieval (Table 1), none of which found that GABA_A PAMs impaired raw 'know' responses. We applied the IRK procedure to these data to see if these studies underestimated drug effects on familiarity.

Methods

Literature Search—We conducted a literature search on PubMed and Google Scholar using the terms 'recollection familiarity,' 'recollective experience,' 'conscious recollection,' or 'remember know' with 'GABA_A positive allosteric modulator,' classes of GABA_A PAMs (e.g., alcohol, benzodiazepines, hypnotics), or specific examples of GABA_A PAMs (e.g., lorazepam, triazolam, zolpidem). References from included studies were reviewed as well. This search yielded 11 studies in which GABA_A PAMs were administered prior to encoding, and the remember/know procedure was used at retrieval (Table 1).

Computations—All memory responses (i.e., ‘remember,’ ‘know,’ ‘guess’ when included, and the sum of these responses, ‘old’) were converted to hit rates for studied items (e.g., $p(\text{‘old’}|\text{target})$), false alarm rates for nonstudied items (e.g., $p(\text{‘old’}|\text{lure})$), and bias corrected memory accuracy (hit rates - false alarm rates). ‘Guess’ rates were added to ‘know’ rates, as guessing that an item is old likely relies on a weak familiarity signal. Excluding guess responses did not change the interpretation of the results. Because recollection and familiarity are assumed to be independent, a ‘know’ response is thought to be the probability of familiarity in the absence of recollection. In order to avoid underestimation, IRK familiarity estimates were computed by dividing $p(\text{‘know’})$ by $1 - p(\text{‘remember’})$ for both hit and false alarm rates (Yonelinas, 2002). Measures were averaged across experimental conditions (see SOM for data inclusion and reduction procedures).

Quantitative analyses were modeled after Libby, Yonelinas, Ranganath, and Ragland’s (2013) meta-analysis on the impact of schizophrenia on recollection and familiarity. Analogous their study, we calculated difference scores between GABA_A PAM and placebo conditions for memory accuracy (when false alarm rates were included). It is worth noting, however, that every study in Table 1 implemented minimal delays between encoding and retrieval, thereby opening up the possibility that the GABA_A PAM manipulations also impacted memory retrieval. When drug effects have been isolated to either encoding or retrieval by implementing delays between these phases, encoding manipulations modulate hit rates (e.g., Ballard, Gallo, & de Wit, 2013; Becker et al., 2017; Weafer et al., 2016a), whereas retrieval manipulations increase false alarm rates (Ballard, Gallo, & de Wit, 2014; Doss, Weafer, Gallo, & de Wit, 2018a, 2018b). Indeed, increases in false alarm rates were observed in the drug conditions of some of the studies in Table 1. Therefore, we also analyzed hit rates to ensure that memory impairments were not due to potential drug effects on memory retrieval that could decrease memory accuracy by increasing false alarm rates. To compute Cohen’s *d* for the effects of GABA_A PAMs on hit rates and accuracy (when sufficient measures of variability were provided), standard deviations were pooled across conditions and transformed when appropriate (e.g., for IRK familiarity estimates and accuracy measures). Multiple drugs or doses within a study were each compared to placebo.

Results and Discussion

Figure 1 shows that GABA_A PAMs at encoding consistently reduced measures of both recollection and familiarity. ‘Remember’ hit rates were reduced in all but one study, and IRK familiarity hit rates were reduced in all but two studies. Furthermore, ‘remember’ and IRK familiarity accuracy were reduced across all studies from which an accuracy measure could be computed. It can also be seen that these reductions were sometimes in a dose-dependent manner. The effect sizes of these reductions were large for most recollection measures, and ranged from small to large for familiarity measures. These findings demonstrate the importance of correcting ‘know’ responses when estimating drug effects on familiarity.

Whereas many studies concluded that GABA PAMs at encoding impaired recollection but not familiarity, here we show using the IRK correction that both processes are impaired. This correction is necessary as drug effects on familiarity can be underestimated by not assuming that familiarity can co-occur with recollection (i.e., when a ‘remember’ response is

made). Additionally, without the IRK correction, familiarity can appear inflated by GABA_A PAMs because a ‘know’ response can only be made when a ‘remember’ response was not. This would explain the spurious increases in familiarity in some prior work (e.g., Curran, Gardiner, Java & Allen, 1993; Mintzer & Griffiths, 2000).

Study 2: DPSD Reanalysis of Weafer et al. (2016a)

A recent study by Weafer et al. (2016a) tested the effects of alcohol on either the encoding or consolidation of memories for emotional and neutral pictures. They reported 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). They also found that alcohol administered immediately after encoding enhanced memory (i.e., retrograde facilitation), though this effect was only significant for neutral pictures.

Weafer et al. (2016a) used a cued memory task to target picture recollections that, as we describe below, left open the possibility that familiarity also could have contributed to memory performance. We, therefore, reanalyzed the confidence data using the DPSD model (Yonelinas, 2002) to estimate recollection and familiarity. This allowed us to (1) replicate the findings of Study 1, that pre-encoding alcohol impairs both recollection and familiarity, and (2) see whether post-encoding alcohol also impacts both recollection and familiarity.

Methods

Participants—This study is described elsewhere (Weafer et al., 2016a). Fifty-nine healthy participants (21–30-years-old, 33 males) were recruited from the community. 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/m², 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 women and men, respectively) in the last month. 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 (.7 g/kg for women and .8 g/kg for men) 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 7 to 10 for women and 10 to 14 for men. 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 ($N = 20$, 11 males), one that received placebo during encoding and alcohol during consolidation ($N = 20$, 11 males), and one that received placebo at both time points ($N = 19$, 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. Twenty minutes later, they 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.

Immediately after viewing the encoding stimuli, participants consumed the second serving of gelatin, and remained in the laboratory. For the first two hours after the second dose, they could only listen to music, and afterward, they could watch movies or read until their BAC had fallen below 40 mg/100 ml.

During the retrieval session 48 hours later, 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. Because this test required discrimination between labels that had been studied with an associated picture and those that had been studied without an associated picture, participants could in principle have relied on recollection of the studied picture or heightened familiarity of the test labels associated with studied pictures to make the discrimination. 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—For the purpose of this reanalysis, we focus on estimates of recollection and familiarity from the confidence data during the cued recollection phase. The recognition phase will not be discussed here because it was confounded with the prior cued recollection task and because distributions from the bootstrapping procedure were not normally distributed (see Statistical Analysis below).

To dissociate 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—Alcohol at encoding and alcohol at 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 alcohol at encoding and alcohol at 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 alcohol at encoding and alcohol at 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. We used this procedure in Doss et al. (2018) and found that drug effects on recollection and familiarity from the DPSD and IRK procedure were similar.

Data Availability—Data from this study are available from <https://doi.org/10.17605/OSF.IO/6DPUV>.

Results and Discussion

The distributions of DPSD-based recollection and familiarity estimates from the bootstrapping procedure were all normal, and as can be seen in Figure 1, the estimates of recollection across conditions tracked the estimates of memory accuracy reported by Weafer et al. (2016a), consistent with their argument that this aspect of the task taps into recollection.

Placebo vs. Alcohol at Encoding—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 alcohol at encoding group were reduced compared to the placebo group. The alcohol at 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, consistent with the reanalysis of remember/know studies described above. Additionally, these effects seem to be larger for emotional than neutral items, as was also found in Weafer et al. (2016a).

Placebo vs. Alcohol at Consolidation—Compared to placebo, 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 1b and 2b). This shows that the boost for neutral items reported by Weafer et al. (2016a) was associated with increases in both recollection and familiarity. By contrast, alcohol after encoding did not affect negative (95% CI: [−.31, .34], $p > .250$) or positive (95% CI: [−.31, .35], $p > .250$) familiarity estimates. Consistent with Weafer et al., alcohol during consolidation did not significantly affect negative (95% CI: [−.11, .15], $p > .250$) or positive recollection estimates (Figure 1c; 95% CI: [−.05, .22], $p = .107$).

General Discussion

These reanalyses demonstrate that alcohol and other GABA_A PAMs during either encoding or consolidation (alcohol only) impact both recollection and familiarity. Whereas these effects have been reported using measures of recollection (e.g., Table 1; Mednick et al., 2013; Weafer et al., 2016a), our findings indicate that the effects of GABA_A PAMs also apply to familiarity. By applying the IRK procedure, we demonstrated that these drugs at encoding also impair familiarity. Moreover, by applying the DPSD analysis to the Weafer et al. (2016a) dataset, we confirmed the encoding findings uncovered with the IRK procedure and also provided the first demonstration that alcohol administered immediately after encoding can enhance familiarity.

The effects of alcohol on encoding are consistent with reports that midazolam at encoding attenuates the neural correlates of both recollection and familiarity (Nyhus & Curran, 2012; Veselis et al., 2009). GABA_A PAMs may reduce familiarity by attenuating semantic or implicit memory processes that are thought to support feelings of familiarity (Yonelinas, 2002; also see Wang et al., 2014; Davies et al., 2004). Although GABA_A PAMs do not always 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 the reanalysis of Weafer et al. (2016a) 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 extra-hippocampally (e.g., perirhinal cortex; see Wang et al., 2014 and Yonelinas et al., 2010). Moreover, 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, Shapiro, Williams, & Fenwick, 2013; Mednick et al., 2013) and increasing the accompanying hippocampal replay that is thought to support the stability of recollections (Rasch & Born, 2008). Because Weafer et al. used a 48-hour delay between encoding and retrieval and because alcohol can alter sleep even hours after consumption (Ebrahim et al., 2013), it is possible that alcohol affected sleep-based consolidation processes during the first night.

One somewhat perplexing finding from Weafer et al. (2016a) and the present reanalysis was that post-encoding alcohol significantly enhanced neutral but not emotional memory, whereas previous work has found effects on emotional memory (Bruce & Pihl, 1997; Bruce, Shestowsky, Mayerovitch, & Pihl, 1999; Knowles & Duka, 2004; Kaestner, Wixted, & Mednick, 2013). There were many methodological differences between studies, including different drugs, doses, and retention intervals that might have interacted with drug effects on emotional memory. Additional work is needed to understand the impact of different GABA_A PAMs on the consolidation of emotional episodic memory.

In summary, we have shown that alcohol and pharmacologically similar sedatives impact both recollection and familiarity, and they do so in different ways at encoding and consolidation. The effects at encoding were notably more robust than those at consolidation. Such global impairments of recollection and familiarity at encoding may speak to anecdotes of ‘blacking out’ from acute intoxication by GABA_A PAMs, even in the presence of an emotional event. These 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. Collectively, the findings across these studies highlight the importance of differentiating drug effects on recollection and familiarity, as well as how the administration of drugs during different stages of episodic memory can impact these processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Difference scores computed from studies in Table 1 between GABA_A positive allosteric modulator (PAM) at encoding and placebo conditions for **a.** ‘remember’ hit rates (R Hit), independence remember/know familiarity hit rates (IRK F Hit), **b.** ‘remember’ accuracy (R Acc), and independence remember/know familiarity accuracy (IRK F Acc). Negative-going bars indicate drug-induced impairment. 1 = Curran et al., 1993 (lorazepam 2 mg), 2 = Bishop & Curran, 1995 (lorazepam 2 mg), 3 = Curran & Hildebrandt, 1999 (alcohol .26/.28 g/kg for females and males), 4 = Milani & Curran, 2000 (alcohol .26/.28 g/kg), 5a-5b = Mintzer & Griffiths, 2000 (triazolam .125 and .25 mg/70 kg), 6 = Duka et al., 2001 (alcohol .8 g/kg), 7a-7b = Huron et al., 2001 (lorazepam .038 and diazepam .3 mg/kg), 8a-8b = Huron et al., 2002 (lorazepam .026 and .038 mg/kg), 9 = Hirshman et al., 2002 (midazolam .03 mg/kg intravenous), 10a-10c = Bisby et al., 2010 (alcohol .4, .6, and .8 g/kg), 11 = Reder et al., 2013 (midazolam .03 mg/kg IV).

Figure 2.

Distributions of **a.** negative, **b.** neutral, and **c.** positive dual process signal detection recollection estimates generated from the bootstrapping procedure on the cued recollection confidence data from Weafer et al., 2016a.

Figure 3.

Distributions of **a.** negative, **b.** neutral, and **c.** positive dual process signal detection familiarity estimates generated from the bootstrapping procedure on the cued recollection confidence data from Weafer et al., 2016a.

Table 1.

Remember/know data from eleven studies using GABA_A PAM challenges during encoding. Measures include hit rates, false alarm rates, and accuracy (hit rates - false alarm rates) for 'old' responses ('remember' and 'know' responses), 'remember' responses, 'know' responses, and familiarity estimates after the independence correction. Approximate *N*s indicate that only full sample size was provided, and therefore, full sample size was divided by number of groups. Blanks indicate that these data were not provided in the original study. Two doses of alcohol within a row indicate doses for females and males, respectively. All drugs can be assumed to be oral unless otherwise stated. R = remember, K = know, IRK F = independence remember/know familiarity, FA = false alarm, Acc = accuracy, PLA = placebo, LOR = lorazepam, ALC = alcohol, TRI = triazolam, DIA = diazepam, MID = midazolam, IV = intravenous.

	<i>p</i> ('old')		<i>p</i> ('R')		<i>p</i> ('K')		IRK F		Acc	R Acc	K Acc	IRK F Acc
	Hits	FAs	Hits	FAs	Hits	FAs	Hits	FAs				
Curran et al., 1993 (<i>N</i> = 12)												
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 (<i>N</i> = 12)												
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	.70
Curran & Hildebrandt 1999, (<i>N</i> = 16)												
PLA	.72	.08	.43	.01	.28	.07	.50	.07	.64	.42	.21	.43
ALC (.26/.28 g/kg)	.51	.04	.26	.01	.26	.03	.34	.03	.48	.25	.22	.31
Milani & Curran, 2000 (<i>N</i> = 20)												
PLA	.74	.03	.51	-	.23	-	.47	-	.71	-	-	-
ALC (.26/.28 g/kg)	.72	.02	.51	-	.21	-	.43	-	.70	-	-	-
Mintzer & Griffiths, 2000 (<i>N</i> = 24)												
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 (<i>N</i> = 12)												
PLA	.34	.07	.23	-	.11	-	.14	-	.27	-	-	-

	$p(\text{'old'})$		$p(\text{'R'})$		$p(\text{'K'})$		IRK F		Acc	R Acc	K Acc	IRK F Acc
	Hits	FAs	Hits	FAs	Hits	FAs	Hits	FAs				
ALC (8 g/kg)	.37	.06	.17	-	.21	-	.25	-	.31	-	-	-
Huron et al., 2001 (N= 12)												
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 (N= 11)												
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 (.38 mg/kg)	.61	.02	.33	.01	.28	.01	.42	.01	.59	.32	.27	.41
Hirshman et al., 2002 (N= 36)												
PLA	.58	.35	.26	.09	.31	.26	.42	.28	.23	.18	.05	.14
MID (.03 mg/kg IV)	.40	.32	.15	.12	.25	.20	.29	.23	.09	.04	.05	.06
Bisby et al., 2010 (N= ~17)												
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 (N= ~10)												
PLA	.47	.11	.24	.04	.23	.08	.30	.08	.36	.21	.15	.22
MID (.03 mg/kg IV)	.37	.20	.17	.08	.20	.12	.24	.13	.17	.09	.08	.11

Table 2.

Six studies from which we were able to compute Cohen's d to compare GABA_A PAMs and placebo at encoding on recollection and familiarity hit rates and accuracy (when false alarm rates were available). Negative effect sizes indicate drug-induced impairment. Two doses of alcohol within a row indicate doses for females and males, respectively. R Hit = remember hit rates, IRK F Hit = independence remember/know hit rates, R Acc = remember accuracy, IRK F Acc = independence remember/know accuracy, LOR = lorazepam, ALC = alcohol, TRI = triazolam, DIA = diazepam.

	R Hit d	IRK F Hit d	R Acc d	IRK F Acc d
Bishop & Curran, 1995 (LOR 2 mg)	-.71	-.32	-.74	-.32
Curran & Hildebrandt, 1999 (ALC .28/.26 g/kg)	-1.02	-.91	-.99	-.42
Milani & Curran, 2000 (ALC .26/.28 g/kg)	.00	-.28	-	-
Duka et al., 2001 (ALC .8 g/kg)	-.49	.96	-	-
Huron et al., 2001 (LOR .038 mg/kg)	-.89	.21	-1.01	-.40
Huron et al., 2001 (DIA .3 mg/kg)	-1.35	-.35	-1.35	-.25
Huron et al., 2002 (LOR .026 mg/kg)	-.91	-1.50	-.84	-.60
Huron et al., 2002 (LOR .038 mg/kg)	-1.87	-2.02	-1.86	-.84