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ORIGINAL INVESTIGATION

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Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve

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Abstract *Rationale:* Little is known about acute effects of alcohol on memory encoding and retrieval on different limbs (ascending and descending) of the blood alcohol concentration (BAC) curve. *Objectives:* This extensive experiment was designed to examine alcohol's effects on memory encoding and retrieval throughout a protracted drinking episode. *Methods:* In a 9-h session, male participants consumed either alcohol (1 ml/kg) or placebo (n= 32/32) over a period of 90 min and learned various materials in different memory tasks before, during, and after consuming the drinks, while their BAC levels were monitored. A week later, in a similar session, they were tested on learned materials before, during, and after drinking. Mood was assessed throughout both sessions. *Results:* Alcohol impaired recall of words more than recognition, and cued recall most severely. Perceptual priming and picture recognition were not affected by alcohol. Alcohol impaired encoding in cued recall, recognition of completed word fragments, and free recall regardless of limb, but impaired retrieval in word recognition only during the ascending BAC. Alcohol increased negative mood on the descending limb during the first session, and on the ascending limb during the second session. *Conclusions:* Under naturalistic drinking conditions, alcohol's effects on memory depend on task, memory process, and limb of the BAC curve. The differential effects of alcohol on retrieval during the ascending and descending limbs demonstrate the importance of examining the differential effects on the two limbs.

Keywords Alcohol · Memory · Encoding · Retrieval · Mood · Ascending · Descending · Limb

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Introduction

Psychopharmacological research on alcohol's acute effects on memory is relevant for understanding the cognitive impairments produced by one of the most widely enjoyed and abused drugs in western cultures. Research on alcohol is also relevant to basic questions about human memory function. Cognitive psychology has strongly influenced research on alcohol and human memory, and alcohol has been found to impair performance in certain memory tasks while leaving that in others unaffected. Episodic memory (Tulving 1972, 1983) is particularly impaired by alcohol (Hashtroudi et al. 1984; Nilsson et al. 1989; Curran and Hildebrandt 1999), semantic retrieval is somewhat less so (Hartocollis and Johnson 1956; Wendt and Risberg 2001), whereas priming (i.e., "the facilitated identification of perceptual objects from reduced cues as a consequence of a specific prior exposure to an object"; Schacter 1994) is regularly unaffected (Fillmore et al. 2000; Hashtroudi et al. 1984; Nilsson et al. 1989; Duka et al. 2001).

Although sophisticated tasks have been used to assess alcohol's effect on different aspects of memory, the pharmacological and metabolic characteristics of alcohol have received less attention. The procedure for administering alcohol is crucial, because alcohol has complex effects on neurotransmission in different brain regions depending on variations in dose, rate and route of administration, and other variables that can produce neural excitation, depression, or both (Eckardt et al. 1998). The conclusions drawn from previous research are mainly based on paradigms where a bolus dose of alcohol has been consumed in less than 30 min (but see Ilan and Gevins 2001) and where only one or two forms of memory were assessed at one point of the blood alcohol concentration (BAC) curve, usually at peak. These experiments have thrown little light on the effects of alcohol at different points on the ascending and descending limbs of the BAC curve, although differential effects of the two limbs on cognition, mood, and physiological responses have been published. Memory, abstract reasoning, attention, and reaction/anticipation time have been found to be impaired on the ascending limb (Hurst and Bagley 1972; Jones and Vega 1972; Jones 1973; Nicholson et al. 1992), a limb usually associated with an increase in skin conductance (Pishkin et al. 1983), arousal and positive mood, but also with aggression. The descending limb usually produces sedation, negative mood (Babor et al. 1983; Sutker et al. 1983; Lukas et al. 1986; Giancola and Zeichner 1997; Papineau et al. 1998; Erblich and Earleywine 2003), and impaired executive function (Pihl et al. 2003). However, the biphasic effects of alcohol on mood, psychomotor/cognitive performance, and heart rate can vary between individuals depending on their family history and drinking habits (Conrod et al. 1997; Hiltunen 1997; Holdstock and de Wit 1998; King et al. 2002).

Alcohol usually impairs episodic memory encoding more than episodic memory retrieval (e.g., Goodwin et al. 1969; Birnbaum et al. 1978; Petersen 1977; but see Fillmore et al. 1999), although few studies have made explicit comparisons between the two processes. Encoding and retrieval often take place during the same drinking session, making it difficult to draw conclusions about alcohol's differential effect on the two processes.

The purpose of the present study was to examine alcohol's effect on memory encoding and retrieval with a 1-week retention interval. In addition, alcohol was administered gradually, as it might be consumed in social drinking situations. Subjects were assessed throughout the whole BAC curve using four different memory tasks. During day 1, or the "study session", subjects studied different materials at eight different times across a 9-h session. On day 8, a week later, subjects were tested for the studied materials during a comparable session, the "test session". By combining data from the study and test sessions, both encoding and retrieval were assessed while subjects were sober, on the ascending limb, at peak, and on the descending limb of the BAC curve. A control group was included that followed the exact same procedure, only without alcohol, to control for sequential effects, practice, and fatigue. Mood was assessed across the BAC curve during both sessions.

We expected that alcohol would differentially affect the memory tasks, impairing episodic memory, but not priming. Within episodic memory, performance in free recall should be the most impaired, given that this task offers the fewest cues at retrieval. Further, as previously shown using other memory tasks, alcohol should impair encoding more than retrieval and lead to worse performance on the ascending limb than on the descending limb at equivalent BACs.

Methods

Subjects

Sixty-four men between 21 and 29 years of age (M, 22.8; SD, 2.4) were recruited from universities in the Washington DC area and paid to participate in the study. Only men were included to eliminate the risk of giving alcohol to pregnant women. Prior to inclusion, subjects were screened for drinking habits, and a psychiatrist screened them to exclude persons with medical and/or psychiatric problems. Subjects reported consuming an average of 3.9 (±2.1) drinks, 2.3 (±1.4) times per week. Drinking frequency ranged from once a month (one person) to once a day (one person), with a median of once to twice a week. Written informed consent was obtained in accordance with the IRB approved protocol.

Subjects were randomly assigned to either the alcohol or placebo group, with 32 persons in each. The two groups did not differ in terms of age, alcohol consumption, or intelligence score (Shipley 1940; cf. Zachary 1986). The placebo group was slightly more educated than the alcohol group [$F_{(1,62)}$=3.9, p=0.05], but the two groups had equivalent sober memory performance.

Design

On day 1, subjects studied one eighth of the materials from each task during each of eight successive study periods (SPs), initiated at the same time points for all subjects, and lasting approximately 25 min. In the alcohol group, these corresponded to (see Fig. 1a): (1) 60 min before the first drink (−60 min), (2) 25 min before the first drink (−25 min), (3) low-ascending BAC (~0.03 g/100 ml; +10 min), (4) high-ascending BAC (~0.06 g/100 ml; +60 min), (5) peak BAC (~0.08 g/100 ml; +120 min), (6) high-descending BAC (~0.06 g/100 ml; +200 min), (7) low-descending BAC (~0.03 g/100 ml; +315 min), and (8) zero BAC (<0.01 g/100 ml; +440 min).

A week later, subjects had a second identical drinking episode and were tested on the materials they had studied the week before. Because test procedures were longer than study procedures, the tasks could not be administered as many times at test (day 8) as they were at study (day 1). Accordingly, all four tasks were performed while subjects

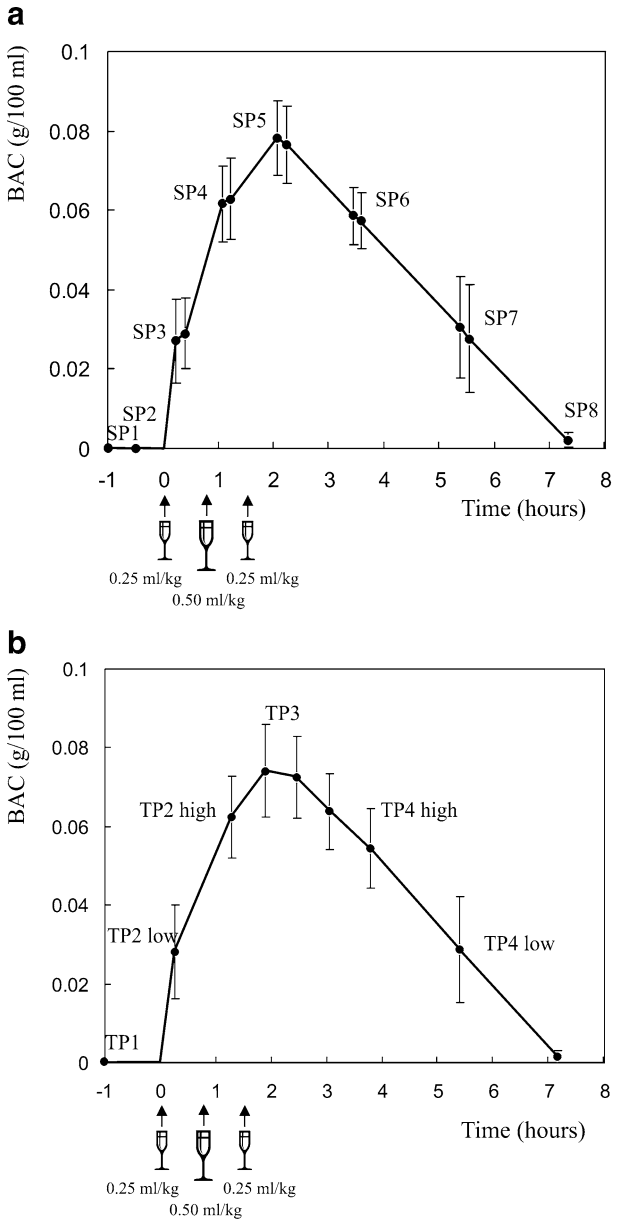

Fig. 1 **a** Blood alcohol concentration during study. The figure shows average *BAC* (*error bars* represent the standard deviations) after the first and before the last memory task at each study period (*SP*) of day 1. The *three glasses* represent alcohol intake, which occurred at time 0, 45, and 90 min. **b** Blood alcohol concentration during test. The figure shows average *BAC* (*error bars* represent the standard deviations) assessed in the middle of each test period (*TP*) of day 8. For TP3, BAC was also assessed before and after testing (see text). The word fragment completion and free-recall tasks were administered on the low rising and falling BAC (~0.03 g/100 ml; "TP2 low" and "TP4 low"), and the associative learning and picture recognition tasks were administered on the high rising and falling BAC (~0.06 g/100 ml; "TP2 high" and "TP4 high"). The *three glasses* represent alcohol intake, which occurred at time 0, 45, and 90 min

were sober (−60 min), only once on the ascending limb (either at low or high BAC; +10 or +60 min), at peak BAC (+110 min), and once on the descending limb (either at low or high BAC; +200 min or +315 min; see Fig. 1b). Like the study periods on day 1, test periods (TPs) occurred at the same time points for all subjects.

Using this approach, the eight study periods were orthogonally combined with four test periods to yield 7-day retention data for each of the four tasks, resulting in 32 study/test combinations. The 32 combinations systematically varied within each subject with respect to the subject's BAC at study (sober, ascending limb, peak, descending limb, and sober postintoxication) and at test (sober, ascending limb, peak, descending limb). This design permitted us to examine alcohol's effects on memory through an expanded, yet finely meshed, window.

A control group went through identical procedures but under placebo conditions to control for factors such as fatigue and interference from the massive amount of materials.

Alcohol administration and BAC assessment

The alcohol group received 1 ml absolute alcohol/kg body weight in a double-blind procedure, divided into three drinks with 5 min given for the consumption of every 0.25 ml/kg of alcohol: 0.25 ml/kg at time 0–5 min (immediately after SP2 and TP1; see Fig. 1a,b), 0.50 ml/kg at time 45–55 min, and 0.25 ml/kg at time 90–95 min. Ten minutes after each of the three drinks, subjects gargled with water, and breath samples were taken using a Mark 4 Gas Chromatographic Intoximeter. Alcohol drinks consisted of one part 95% ethanol and seven parts peppermint-lemonade masking solution. Masking solution was Minute Maid Crystals at 150% recommended solution with 1.0 ml peppermint extract per liter solution. The placebo group received the same volume of masking solution with 0.25 ml alcohol floated on top of each drink to give olfactory cues of alcohol. All participants were told they might receive varying doses of alcohol during one of the sessions or both. Although it is hard to simulate a high alcohol dose, or to mask it, the possibility of receiving alcohol, the alcohol smell of the placebo drink, and the repetitive BAC readings contributed to increase expectancy. The efficacy of the placebo condition was assessed by asking participants to rate how "high" they felt (ranging between 0=not at all high and 5=extremely high) and how many drinks it would take to make them feel the way they did (ranging between 0 and 12 or more drinks). This was done repeatedly throughout both sessions, in association with the mood questionnaire described below.

At each study period, BAC was assessed twice, the first following the first memory task and the other preceding the last. At test, BAC was assessed between tasks during TPs 2 low, 2 high, 4 high, and 4 low. TP3 covered all tasks and was longer than TPs 2 and 4. BAC was therefore assessed before, in the middle of, and after testing during this test period.

Memory tasks

Four different memory tasks were included to assay a wide range of mnemonic processes. Tasks were selected to be memorable a week later in the context of a vast amount of other potentially interfering materials and sufficiently interesting to engage the attention of intoxicated subjects during two 9-h experimental sessions.

The materials of each memory task were organized into 32 subsets. Four subsets of materials were studied during each of the eight study periods on day 1, and one subset from each study period was tested during each of the four test periods a week later. The 32 subsets were counterbalanced across study and test periods. Detailed information about the number of stimuli presented at each study period and test period is shown in Table 1, and brief descriptions of test procedures and administration time are provided in Table 2.

Associative learning (recognition and cued recall) This task is a variant of the traditional paired-associate task typically used to assess associative learning. Each test item consisted of a humorous unfamiliar "definition" of a familiar noun, followed by the noun in question (e.g., a wide sphere cracks its skin—EARTHQUAKE). The definition part of the test item serves as the "cue" at test, and the noun as the "target" (i.e., material to remember) to first be recognized and then recalled (Tulving and Watkins 1977). This task was included inasmuch as the unique phrases have been shown to be memorable for a long time after study (Hayman et al. 1993) and are frequently used in cognitive psychology and neuropsychology. Half of the test items were randomly categorized as cue–target pairs, presented during both study and test, and half served as distractor pairs (i.e., lures), presented only during test.

At study, subjects were asked to rate on a four-point scale how much sense each definition made for the word in question. At test, each previously encountered cue–target pair, together with new similar distractors, was tested twice, first for recognition from day 1 of the target word without the cue (EARTHQUAKE—yes or no?), and then for cued recall of the same target word (a vast sphere cracks its skin—which word?). During cued recall, if subjects were unable to explicitly recall the target, they were encouraged to guess.

Recognition was scored in terms of "hits" ("yes" responses to studied target words) and "false alarms" ("yes" responses to nonstudied distractor words). The difference between the proportions of hits and false alarms reflects what subjects remember from the study list. A subject's cued recall score (proportion of correct target words produced to cues), in this design, reflects the combined effects of (1) associative learning retained over 7 days and (2) correct matching ("lucky guesses") of the target words, remembered from the preceding recognition test, to their respective cues. Because such lucky guessing is assumed to be comparable for the originally studied and nonstudied items, the difference in the cued recall scores between targets and distractors provides an estimate of cued (associative) recall.

Picture recognition At study, subjects viewed complex color photographs, selected from National Geographic and from earlier studies on alcohol (cf. Parker et al. 1976, 1980; Tulving 1981). At test, subjects performed a forced-choice recognition task where they chose which of two slides they had seen on day 1. To make retrieval more difficult, each target photograph was paired with a highly similar distractor. The picture pairs were pilot tested to ensure that the 32 subsets were equally difficult.

Word fragment completion (perceptual priming and recognition) This task consisted of completing single-solution word fragments (e.g., A_ _ A _ _ IN). The materials were words having three or four letters missing in their most fragmented form. At both study and test, the fragments were presented through ascending method of limits (cf. Snodgrass and Feenan 1990), with missing letters being successively added until the subject came up with the word (e.g., ASSASSIN). Completion difficulty was matched in the 32 subsets of materials based on pilot testing. At test, subjects were tested for their ability to complete the same fragments they completed during study (targets) along with new fragments (distractors), and after each completion, they were tested on their recognition of the words generated from the fragments. Priming was defined as the proportion of completed target fragments on day 8 minus the proportion of completed distractor fragments. Recognition was assessed in terms of hits and false alarms.

Free recall Because the present design required materials from certain study periods to be retrieved at certain test periods, it precluded the use of a traditional free recall task and called for a way to direct subjects what materials to retrieve. Accordingly, a modified free recall task was developed, with 24 words drawn from each of four semantic categories (the 3rd to the 26th most frequent

Table 1 Number of stimuli in the memory tasks as a function of study period, test period, and in total

Memory task	Stimuli per study period	Stimuli per test period		Total Stimuli	
		T	D	T	D
Associative learning	16	32	32	128	128
Picture recognition	24	48	48	192	192
Word fragment completion	16	32	16	128	64
Free recall	12	24	NA	96	NA

All stimuli in a specific task were distributed across eight study periods and four test periods. For example, for associative learning, 16 stimuli were presented during each of the eight study periods (128 stimuli total). During each of the four test periods, 32 previously studied stimuli were presented as targets and 32 novel stimuli were presented as distractors

T targets, *D* distractors, *NA* not applicable

Table 2 Procedure and distribution time of memory measures at study and test

Memory measure	Procedure at study	Distribution time at study (per item and in total)	Procedure at test	Distribution time at test (per item and in total)
Associative learning (recognition/cued recall)	Read phrase–word pairs and rate how much sense they make	8 sec/pair; 3 min total	Recognition: judge whether a presented word is old or new	Recognition: 5 sec/word; 6 min total
			Cued recall: come up with a word given the phrase	Cued recall: 8 sec/phrase; 9 min total
Picture recognition	Watch photos	5 sec/photo; 2.5 min total	Chose from two similar photos which one was seen before	10 sec/pair; 9 min total
Word-fragment completion (priming/ recognition)	Complete word fragments	8 sec/fragment slide; 11 min total	Priming: complete word fragments Recognition: judge whether completed word is old or new	8 sec/fragment slide; 27 min total
Free recall	Rank words according to certain semantic criteria followed by immediate recall	10 sec/triad; 1 min total	Recall words given the category cue, one category per test period	3 min per category; 3 min total (i.e., one category tested per test period)

Total distribution times include instructions

category exemplars; Battig and Montague 1969). During each study period, three words from each of the four categories were presented (12 in total; see Table 1). Subjects were asked to rank these words according to a certain criterion (e.g., professions in terms of salary), and thereafter write down the words. On day 8, during each of the four test periods, one of the category names (counterbalanced across test periods) was given to indicate what words to retrieve. At each test period, participants could thus recall three words from each of the eight study periods, 24 words in total. The proportion of recalled words was the measure of performance.

Associative learning and picture recognition were tested at the high BAC, whereas perceptual priming and free recall were tested at the low BAC. The rationale for this allocation was that (1) the free recall task was expected to be the most vulnerable to alcohol because it provides the fewest retrieval cues, and it could therefore be tested at a lower BAC than tasks less sensitive to alcohol; and (2) tasks needed to be grouped so that each test period did not exceed 30 min.

Profile of mood states

Mood was assessed throughout the study and test periods (except at SP2) by means of the profile of mood states (POMS) (McNair et al. 1971). This mood scale consists of 65 items where participants rate their state of mind (e.g., friendly, nervous) on a scale between 0 (not at all) and 4 (extremely). Six mood scores are obtained: tension, depression, anger, vigor, fatigue, and confusion. Most subjects took about 3 min to complete the scale. Although this activity constituted a diversion for the subjects, it was brief and easy enough not to tax their resources.

Procedure

Subjects agreed to refrain from alcohol and other psychoactive substances for 48 h and to fast from midnight onward before each experimental session. They arrived at the laboratory at 8 a.m. and were interviewed about compliance with instructions. A baseline breath sample was taken to ensure sobriety. Alcohol was given on an empty stomach to reduce the variability in BAC among subjects. Caloric intake was provided in the large volume of concentrated lemonade masking solution. Subjects performed the tasks in groups of two or four with an alcohol subject and his yoked placebo subject going through the sessions together. They brought their own lunch which they were allowed to eat after SP5 of day 1 and TP3 of day 8. Because alcohol is metabolized at a rate constant (Grilly 1998), differences in caloric content of the lunch should not cause variability in BAC during the study and test periods after peak. Breath samples were taken at the end of both

sessions to verify sobriety. The sessions lasted approximately 9 h, and subjects left the laboratory when BAC had reached zero.

Analyses

The eight study periods and four test periods gave rise to 32 measurement points. Mixed-design ANOVA was used for all analyses, with group as between-subjects factor (alcohol vs placebo) and study and test periods as within-subjects factors. Depending on the issue under examination, different points of the 8×4 study and test period matrix were included. A detailed description of the specific analyses is provided for the recognition part of the associative learning task, and the same analyses were performed on all the other tasks. No adjustment was made for initial performance, because the groups had equivalent sober peformance (see SP1/TP1 in Tables 3, 4, 5), tested by *t* tests.

Results

Alcohol expectancy

The alcohol group felt significantly "higher" than the placebo group (assessed through *t* tests, *ps*≤0.003) at study periods 4 through 7 and test periods 2 low through 4 low. At study, the alcohol group's high scores were 2.2, 2.3, 1.8, and 0.7, respectively, whereas the placebo group's high scores were 0.9, 0.5, 0.2, and 0.1, respectively. At test, the alcohol group's high scores were 1.4, 2.5, 2.1, 1.0, and 0.7 whereas the placebo group had scores of 0.3, 0.5, 0.2, 0.2, and 0.1. Although the differences in high were significant between the two groups, the placebo group's average high scores were all above zero. The alcohol group estimated they had had more to drink than the placebo group at study periods 3 through 6, and test periods 2 high through 4 low (*ps*≤0.006). Nevertheless, through study periods 3 to 6, 47, 50, 28, and 6%, respectively, of the subjects in the placebo group believed they had had some alcohol (ranging between one and four drinks). At test, these values were 16, 16, 6, and 6%, respectively.

Associative learning

Recognition (EARTHQUAKE?)

Overall effects of alcohol Alcohol's overall effects were assessed using mixed design 2 (Group) ×5 (SP 3–7) ×3 (TP 2–4) ANOVAs (see the values in bold in Table 3 and corresponding tables for the other memory measures). These study and test periods were included because the alcohol group and the placebo group differed in BAC during these periods. The number of recognition hits showed a tendency of an overall effect of alcohol [$F_{(1,62)}$=3.51, p=0.07] where the alcohol group generally

Table 3 Recognition of words in the associative learning task, Mean (SD) proportion of hits and false alarms in the placebo and alcohol groups as a function of study and test periods and the BACs (g/100 ml) in the alcohol group corresponding to that study or test period

Test period and BAC			Study period and BAC									
			SP1 0.00	SP2 0.00	SP3 0.03 asc.	SP4 0.06 asc.	SP5 0.08 peak	SP6 0.06 desc.	SP7 0.03 desc.	SP8 0.00	Mean hits (test)	Mean false alarms
TP1	0.00	P	0.66 (0.23)	0.66 (0.30)	0.65 (0.25)	0.68 (0.25)	0.56 (0.27)	0.66 (0.25)	0.63 (0.27)	0.75 (0.24)	*0.66 (0.16)*	*0.39 (0.16)*
		A	0.73 (0.26)	0.69 (0.26)	0.72 (0.24)	0.66 (0.27)	0.66 (0.22)	0.66 (0.24)	0.75 (0.22)	0.73 (0.27)	*0.70 (0.14)*	*0.43 (0.16)*
TP2	0.06 asc.	P	0.74 (0.24)	0.80 (0.21)*	**0.77 (0.28)***	**0.74 (0.23)§§**	**0.75 (0.22)***	**0.69 (0.27)**	**0.66 (0.24)**	0.65 (0.26)	*0.72 (0.15)†*	*0.41 (0.19)*
		A	0.69 (0.26)	0.64 (0.32)	**0.59 (0.27)**	**0.50 (0.30)**	**0.61 (0.28)**	**0.60 (0.31)**	**0.57 (0.28)**	0.70 (0.26)	*0.61 (0.18)*	*0.39 (0.12)*
TP3	0.08 peak	P	0.72 (0.27)	0.67 (0.32)	**0.72 (0.30)**	**0.72 (0.26)**	**0.66 (0.30)**	**0.70 (0.27)**	**0.68 (0.27)**	0.70 (0.26)	*0.70 (0.19)*	*0.42 (0.22)*
		A	0.63 (0.31)	0.70 (0.25)	**0.60 (0.28)**	**0.66 (0.24)**	**0.59 (0.23)**	**0.63 (0.27)**	**0.64 (0.28)**	0.67 (0.26)	*0.64 (0.16)*	*0.44 (0.15)*
TP4	0.06 des.	P	0.68 (0.25)	0.70 (0.28)	**0.65 (0.31)**	**0.63 (0.32)**	**0.66 (0.25)**	**0.63 (0.32)**	**0.70 (0.21)**	0.63 (0.32)	*0.66 (0.18)*	*0.42 (0.20)*
		A	0.81 (0.21)*	0.67 (0.29)	**0.70 (0.25)**	**0.66 (0.27)**	**0.59 (0.29)**	**0.64 (0.30)**	**0.64 (0.31)**	0.63 (0.29)	*0.67 (0.19)*	*0.46 (0.17)*
Mean hits (study)		P	*0.70 (0.18)*	*0.71 (0.20)*	*0.70 (0.19)*	*0.69 (0.19)*	*0.66 (0.18)*	*0.67 (0.18)*	*0.67 (0.17)*	*0.68 (0.19)*	*0.68 (0.15)*	*0.41 (0.17)*
		A	*0.72 (0.20)*	*0.67 (0.20)*	*0.65 (0.17)*	*0.62 (0.20)*	*0.61 (0.17)*	*0.63 (0.19)*	*0.65 (0.20)*	*0.68 (0.19)*	*0.66 (0.25)*	*0.43 (0.12)*

False alarms are only reported as a function of test period inasmuch as distractors were only presented at test. The values in bold indicate data used in analyses of main effects of alcohol
P placebo, *A* alcohol, *asc.* ascending limb, *desc.* descending limb
*p<0.05; †p<0.01; §p=0.001. The significance symbols mark the group that had the significantly higher performance

Table 4 Cued recall in the associative learning task, Mean (SD) proportion of correctly solved targets and distractors in the placebo and alcohol groups as a function of study and test periods and the BACs (g/100 ml) in the alcohol group corresponding to that study or test period

Test period and BAC			Study period and BAC										
			SP1 0.00	SP2 0.00	SP3 0.03 asc.	SP4 0.06 asc.	SP5 0.08 peak	SP6 0.06 desc.	SP7 0.03 desc.	SP8 0.00	Mean solved targets (test)	Mean solved distractors	Correct. mean solved targets
TP1	0.00	P	0.38 (0.23)	0.41 (0.30)	0.46 (0.24)	0.36 (0.28)	0.34 (0.22)	0.34 (0.30)	0.41 (0.29)	0.36 (0.30)	*0.38 (0.16)*	*0.12 (0.08)*	*0.26 (0.14)**
		A	0.30 (0.26)	0.37 (0.24)	0.35 (0.31)	0.32 (0.26)	0.23 (0.23)	0.27 (0.29)	0.31 (0.26)	0.34 (0.27)	*0.31 (0.17)*	*0.13 (0.08)*	*0.19 (0.14)*
TP2	0.06 asc.	P	0.39 (0.25)*	0.44 (0.32)*	**0.41 (0.28)†**	**0.33 (0.27)**	**0.34 (0.30)†**	**0.34 (0.26)†**	**0.31 (0.28)**	0.38 (0.26)	*0.37 (0.16)‡*	*0.13 (0.08)‡*	*0.24 (0.15)**
		A	0.26 (0.22)	0.27 (0.26)	**0.24 (0.22)**	**0.23 (0.23)**	**0.16 (0.20)**	**0.17 (0.18)**	**0.20 (0.23)**	0.28 (0.23)	*0.23 (0.12)*	*0.06 (0.05)*	*0.17 (0.10)*
TP3	0.08 peak	P	0.33 (0.27)	0.37 (0.30)	**0.35 (0.25)**	**0.33 (0.25)***	**0.27 (0.24)***	**0.41 (0.23)§**	**0.36 (0.24)***	0.41 (0.30)§	*0.35 (0.15)‡*	*0.14 (0.09)§*	*0.22 (0.12)**
		A	0.23 (0.17)	0.23 (0.25)	**0.34 (0.27)**	**0.20 (0.21)**	**0.16 (0.18)**	**0.18 (0.22)**	**0.23 (0.26)**	0.18 (0.22)	*0.22 (0.12)*	*0.07 (0.06)*	*0.15 (0.10)*
TP4	0.06 des.	P	0.37 (0.25)	0.39 (0.25)	**0.41 (0.30)***	**0.39 (0.25)***	**0.38 (0.25)†**	**0.35 (0.26)†**	**0.33 (0.27)**	0.44 (0.25)†	*0.38 (0.14)‡*	*0.14 (0.09)**	*0.24 (0.11)†*
		A	0.26 (0.20)	0.31 (0.21)	**0.27 (0.22)**	**0.24 (0.24)**	**0.22 (0.21)**	**0.17 (0.21)**	**0.24 (0.27)**	0.25 (0.28)	*0.25 (0.13)*	*0.09 (0.07)*	*0.16 (0.10)*
Mean solved targets (study)		P	*0.37 (0.18)**	*0.40 (0.21)**	*0.41 (0.16)†*	*0.35 (0.17)**	*0.33 (0.16)‡*	*0.36 (0.15)‡*	*0.35 (0.16)**	*0.40 (0.18)†*	*0.37 (0.14)‡*	*0.13 (0.06)§*	*0.24 (0.10)§*
		A	*0.26 (0.14)*	*0.30 (0.14)*	*0.30 (0.16)*	*0.25 (0.16)*	*0.19 (0.14)*	*0.20 (0.15)*	*0.25 (0.16)*	*0.26 (0.16)*	*0.25 (0.11)*	*0.08 (0.05)*	*0.17 (0.08)*

The values in bold indicate data used in analyses of main effects of alcohol
P placebo, *A* alcohol, *asc*. ascending limb, *desc*. descending limb, *Correct*. corrected
**p*<0.05; †*p*<0.01; §*p*<0.001; ‡ *p*<0.0001. The significance symbols mark the group that had the significantly higher performance

Table 5 Recognition of completed word fragments, Mean (SD) proportion of hits and false alarms in the placebo and alcohol groups as a function of study and test periods and the BACs (g/100 ml) in the alcohol group corresponding to that study or test period

Test period and BAC			Study period and BAC									
			SP1 0.00	SP2 0.00	SP3 0.03 asc.	SP4 0.06 asc.	SP5 0.08 peak	SP6 0.06 desc.	SP7 0.03 desc.	SP8 0.00	Mean hits (test)	Mean false alarms
TP1	0.00	P	0.91 (0.15)	0.88 (0.17)	0.91 (0.18)	0.90 (0.18)	0.89 (0.18)*	0.89 (0.15)*	0.91 (0.14)	0.91 (0.16)	*0.90 (0.10)*	*0.17 (0.09)*
		A	0.91 (0.15)	0.90 (0.17)	0.87 (0.23)	0.83 (0.20)	0.78 (0.21)	0.80 (0.21)	0.86 (0.18)	0.88 (0.16)	*0.85 (0.13)*	*0.15 (0.08)*
TP2	0.03 asc.	P	0.92 (0.12)	0.93 (0.13)	**0.91 (0.14)**	**0.91 (0.14)†**	**0.90 (0.15)***	**0.92 (0.13)***	**0.91 (0.16)**	0.92 (0.13)	*0.92 (0.07)**	*0.21 (0.12)*
		A	0.92 (0.13)	0.88 (0.18)	**0.88 (0.22)**	**0.77 (0.20)**	**0.76 (0.26)**	**0.83 (0.21)**	**0.84 (0.19)**	0.89 (0.15)	*0.85 (0.13)*	*0.17 (0.09)*
TP3	0.08 peak	P	0.94 (0.13)*	0.87 (0.22)	**0.88 (0.18)**	**0.90 (0.18)**	**0.88 (0.18)***	**0.84 (0.18)**	**0.89 (0.15)**	0.92 (0.13)*	*0.89 (0.09)**	*0.23 (0.11)*
		A	0.83 (0.22)	0.86 (0.23)	**0.83 (0.21)**	**0.83 (0.22)**	**0.76 (0.25)**	**0.77 (0.29)**	**0.84 (0.20)**	0.80 (0.24)	*0.81 (0.17)*	*0.18 (0.08)*
TP4	0.03 des.	P	0.91 (0.22)	0.88 (0.17)	**0.87 (0.17)**	**0.95 (0.12)†**	**0.88 (0.14)**	**0.86 (0.20)**	**0.87 (0.19)**	0.88 (0.18)	*0.89 (0.09)*	*0.24 (0.12)*
		A	0.91 (0.19)	0.88 (0.22)	**0.83 (0.25)**	**0.83 (0.20)**	**0.81 (0.23)**	**0.82 (0.24)**	**0.86 (0.17)**	0.91 (0.16)	*0.86 (0.13)*	*0.21 (0.09)*
Mean hits (study)		P	*0.92 (0.08)*	*0.89 (0.14)*	*0.89 (0.10)*	*0.91 (0.11)§*	*0.89 (0.11)§*	*0.88 (0.11)*	*0.89 (0.10)*	*0.91 (0.10)*	*0.90 (0.08)**	*0.21 (0.10)*
		A	*0.89 (0.13)*	*0.88 (0.16)*	*0.85 (0.17)*	*0.81 (0.13)*	*0.78 (0.17)*	*0.80 (0.18)*	*0.85 (0.13)*	*0.87 (0.12)*	*0.84 (0.13)*	*0.18 (0.06)*

The values in bold indicate data used in analyses of main effects of alcohol
P placebo, *A* alcohol, *asc*. ascending limb, *desc*. descending limb
**p*<0.05; †*p*<0.01; §*p*<0.005. The significance symbols mark the group that had the significantly higher performance

had fewer hits than the placebo group (11% fewer hits on average; see Table 3). There was a significant interaction between group and test period [$F_{(2,124)}$=4.95, p=0.01] due to the alcohol group performing worse than the placebo group on the ascending limb (see Table 3, TP2), but not at the other test periods.

As distractors were presented only at test, false alarms were analyzed in terms of group and test by mixed design 2 (Group) ×3 (TP 2–4) ANOVAs. The proportion of false alarms did not differ between groups (F<1), so there was no need for correction of the hits.

Simple effects of alcohol on encoding and retrieval To assess alcohol's effect on encoding without potential contamination by its effect on retrieval, intoxicated encoding (SP 3–7) and sober retrieval (TP1) were analyzed using a mixed design 2 (Group) ×5 (SP 3–7) ANOVA. In a similar fashion, only sober encoding (SP1) was included to study alcohol's pure effect on retrieval, at TPs 2 to 4 [2 (Group) ×3 (TP 2–4) repeated measures ANOVA]. SP2 was not included because of possible memory enhancement of material encoded just prior to alcohol intake (cf. Parker et al. 1980, 1981). There was no simple effect of alcohol on encoding [$F_{(1,62)}$=1.06, ns] or retrieval (F<1). However, group and TP interacted [$F_{(2,124)}$=5.64, p=0.005] due to the alcohol group performing significantly better than the placebo group on the descending limb (see Table 3, SP1, TP4). Because the alcohol group had higher performance than the placebo group only at this measurement point out of 32 possible points, and because this finding is in opposition with previous research, it may be a spurious finding.

Effects of alcohol on the ascending and descending limbs The marginal means of SPs 3, 4, 6, and 7 and TPs 2 and 4 were included in 2 (Group) ×2 (Limb) mixed-design ANOVAs to compare the effect of alcohol for low and high BACs on the ascending vs. descending limbs at study (SP3 vs. SP7 and SP4 vs. SP6, respectively) and the ascending vs. descending BAC at retrieval (TP2 vs. TP4). An interaction between group (alcohol vs. placebo) and limb (ascending vs. descending) would suggest a differential effect of alcohol on the ascending and descending limbs of the BAC curve. There was no interaction between limb and group at study at either the high or low BAC (Fs<1), but the two factors interacted at retrieval [$F_{(1,62)}$=10.43, p<0.005]. This interaction was due to the alcohol group having fewer hits than the placebo group on the ascending limb at retrieval. There was no interaction between limb and group in terms of false alarms [$F_{(1,62)}$=2.85, p=0.10].

Cued recall (a vast sphere cracks it skin—_____?)

Overall effects of alcohol Identical analyses as those described above revealed a significant overall effect of alcohol on cued recall of target words [$F_{(1,62)}$=20.42, p<0.0001]. As can be seen in Table 4, the alcohol group performed worse than the placebo group throughout all study periods and at test at rising, peak, and falling BAC (39% fewer correctly recalled words on average).

Alcohol also had an overall effect on solving distractor cues (lucky guesses) [$F_{(1,62)}$=19.71, p<0.0001] that were only seen on day 8. Impairment occurred at all test periods where alcohol was present (i.e., TPs 2–4 in Table 4). To get an estimate of pure memory performance that does not comprise the ability to solve the phrase cues through semantic elaboration and/or guessing, the proportions of solved distractor cues were subtracted from the proportions of solved target cues (e.g., the "mean solved distractors" value of TP1 was subtracted from the proportions of solved targets of TP1/SPs 3–7, respectively). Having corrected for the general ability to solve distractors, the effect of alcohol on cued recall remained significant [$F_{(1,62)}$=11.07, p=0.001], although smaller, partial η^2=0.15 as compared to partial η^2=0.25 for uncorrected solved targets.

Simple effects of alcohol on encoding (sober retrieval) and retrieval (sober encoding) Alcohol impaired encoding of materials that were recalled while sober [$F_{(1,62)}$=4.01, p=0.05]. Alcohol also impaired retrieval when study had been sober [$F_{(1,62)}$=7.43, p<0.01], but this effect was no longer significant after correction for distractor solving [$F_{(1,61)}$=1.94, ns]. The retrieval effect of alcohol was thus mainly due to alcohol's detrimental effect on solving cues in general.

Effects of alcohol on the ascending and descending limbs There were no interactions between group and limb either at encoding or retrieval in corrected target solving (Fs<1).

Picture recognition

There was no overall effect of alcohol on picture recognition, nor were there any effects on encoding, retrieval, or any interactions (Fs<1).

Word fragment completion

Perceptual priming The overall completion rates of target and distractor fragments on day 8 were 0.21 and 0.09 in the alcohol group and 0.22 and 0.08 in the placebo group, giving rise to respective priming scores of 0.12 and 0.14. Alcohol had no overall effect on the amount of priming, and no effects were observed in any of the focal analyses (Fs≤1).

Recognition of completed word fragments

Overall effects of alcohol Alcohol reduced the number of hits [$F_{(1,62)}$=7.16, p<0.05], with the alcohol group always having fewer hits than the placebo group (8% fewer hits on average; see Table 5). The rate of false alarms was not affected by alcohol [$F_{(1,62)}$=2.87, p<0.05], so there was no need to adjust hits for false alarms.

Simple effects of alcohol on encoding (sober retrieval) and retrieval (sober encoding) Recognition hits were significantly reduced when subjects encoded under alcohol and retrieved when sober [$F_{(1,62)}$=5.22, p<0.05]. Although alcohol had no main effect on retrieval, group interacted with test period [$F_{(2,124)}$=3.77, p<0.05] due to the alcohol group having fewer hits at ascending and peak BAC at test (TPs 2 and 3; see Table 5).

Effects of alcohol on the ascending and descending limbs There was no interaction between group and limb at study (F<1), but at retrieval, group and limb interacted [$F_{(1,62)}$=4.31, p<0.05] due to the alcohol group having fewer hits than the placebo group on the ascending but not the descending limb. There was no interaction in terms of false alarms between group and limb (F<1).

Free recall

Overall effects of alcohol Alcohol had an overall effect on the number of words recalled [$F_{(1,62)}$=5.97, p<0.05,], globally reducing performance (the average recall was 0.25±0.07 in the alcohol group and 0.30±0.10 in the placebo group).

Simple effects of alcohol on encoding (sober retrieval) and retrieval (sober encoding) There was a significant detrimental effect of alcohol on encoding [$F_{(1,62)}$=6.33, p<0.05], but not on retrieval (F<1). Under conditions of intoxicated encoding and sober retrieval, the alcohol group's average recall was 0.20±0.11, compared to the placebo group's average recall of 0.27±0.10 at the same study and test periods. Under conditions of sober encoding and intoxicated retrieval, the groups' recall was 0.34±0.16 and 0.34±0.20, respectively.

Effects of alcohol on the ascending and descending limbs There was no interaction between group and limb either at encoding or retrieval.

Mood There was no difference between groups in sober mood scores (tested by t tests), so no adjustment was made for baseline mood. At encoding, 2 (Group) ×2 (Limb) mixed-design ANOVAs run separately for low and high BAC revealed differential effects of alcohol on the ascending and descending limbs in the depression, vigor, and fatigue scores as reflected in group × limb interactions (see Fig. 2, left column). At identical BAC (~0.03 g/100 ml), the alcohol group's depression scores were higher on the descending limb than on the ascending limb, in contrast to the placebo group which showed the reverse pattern. The alcohol group's vigor scores were lower on the descending limb than on the ascending limb, whereas there was no difference between limbs in the placebo group. The opposite was true for the fatigue scores, which were higher in the alcohol group on the descending limb (low and high BAC) than on the ascending limb, but were similar in the placebo group. Generally, the alcohol group had somewhat higher scores on tension, fatigue, and confusion. At retrieval, no interactions between group and limb were observed, although the alcohol group generally had somewhat higher tension, anger, and confusion scores than the placebo group, and particularly so on the high ascending limb (see Fig. 2, right column).

Discussion

The present study was undertaken to examine alcohol's effects on memory encoding and retrieval during the ascending and descending limbs of the BAC curve using a new design. The experiment included multiple memory tasks distributed at encoding and retrieval throughout the whole BAC curve when subjects had consumed alcohol gradually, as may occur in social drinking situations. Further, recall took place one week after study, which is a longer retention interval than that used in most studies, providing an estimate of alcohol's effects on long-term memory. Earlier studies have contrasted effects of alcohol on the ascending and descending limbs on different cognitive functions and mood, but this is the first study to examine the effects of cumulative drinking on memory throughout the whole intoxication period, during both encoding and retrieval.

In line with previous research and our expectations, alcohol impaired episodic encoding. This was true for cued recall, recognition of completed word fragments, and free recall. Unexpectedly, alcohol also impaired retrieval in two word recognition tasks (in associative learning and word fragment completion), particularly on the ascending limb of the BAC curve. Previous findings of alcohol-resistant forms of memory, specifically perceptual priming, were replicated in this study, but a lack of alcohol effect was also found in episodic memory for complex pictorial scenes. Contrary to our predictions, the memory measure most impaired by alcohol was cued recall rather than free recall, with the largest effects occurring when both encoding and retrieval took place during intoxication.

Alcohol impaired encoding in three verbal episodic memory tasks (cued recall, recognition of completed word fragments, and free recall). Impaired encoding of verbal materials under alcohol has been observed before with slightly higher alcohol doses (Goodwin et al. 1969; Petersen 1977). Research in rodents has shown that alcohol distorts the function of the hippocampus and the septo-hippocampal pathway (Givens 2000; White 2000) and blocks hippocampal long-term potentiation (Sinclair and Lo 1986; Givens and McMahon 1995). An alteration of hippocampal function may in part be the cause of the reduced encoding and, to a smaller extent, retrieval, given the hippocampus' differential involvement in these two processes (Lepage et al. 1998). Episodic encoding and retrieval also differentially involve the prefrontal cortex (Tulving et al. 1994), which is yet another structure to explore in relation to alcohol-induced memory impairment. However, inferences on the locus of alcohol's impact on the brain made on the basis of behavioral data remain

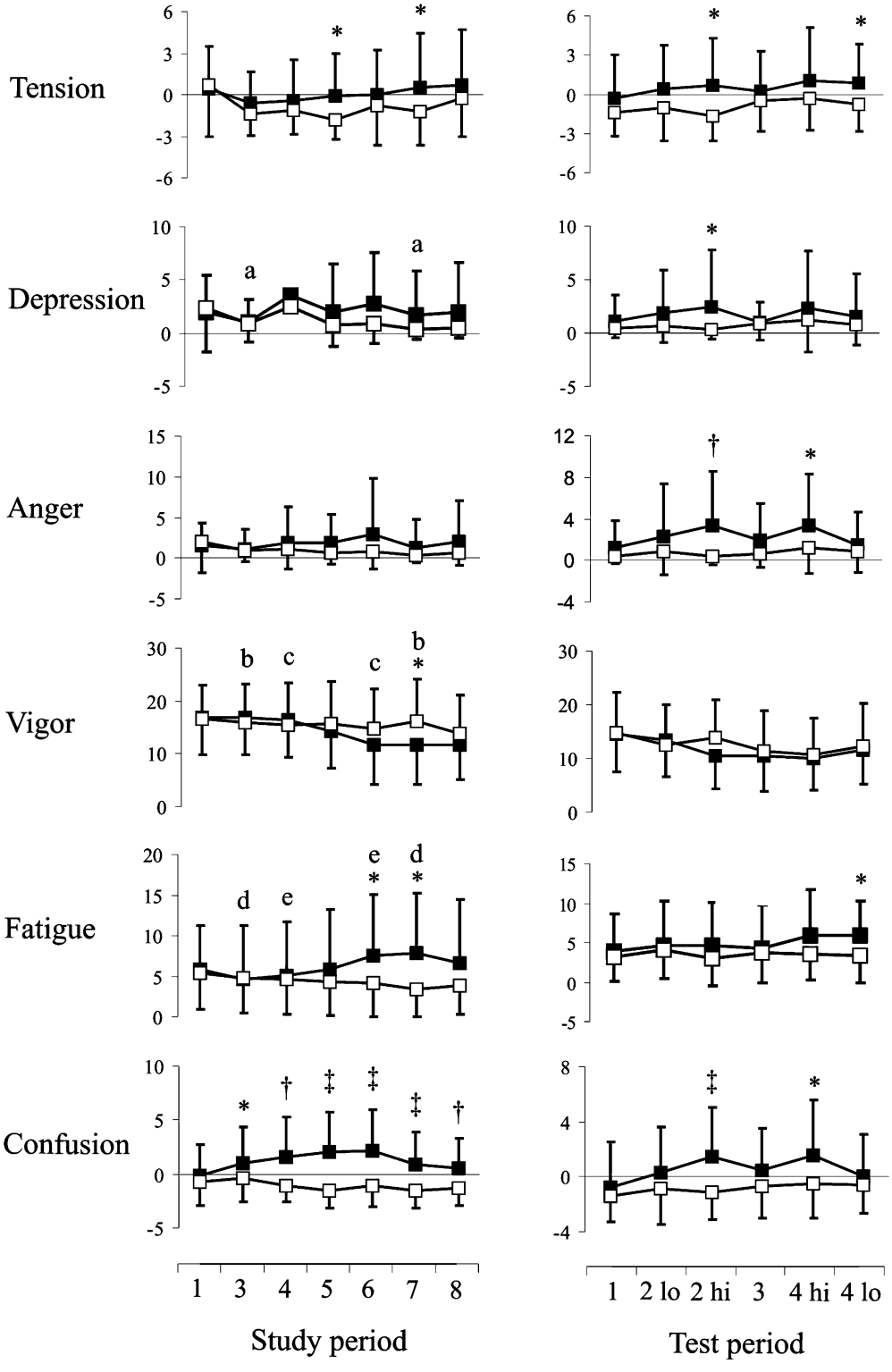

Fig. 2 Average POMS subscores during the different study periods (*left*) and test periods (*right*) in the alcohol group (■) and the placebo group (□). The *error bars* represent the standard deviations and are only shown in one direction for clarity. lo=low, hi=high. Score differences between groups were assessed by *t* tests: **p*<0.05; †*p*<0.005; ‡*p*<0.0001; [a]Group × Limb interaction $F_{(1,60)}$=4.36, *p*<0.05; [b]Group × Limb interaction $F_{(1,61)}$=12.84, *p*<0.005; [c]Group × Limb interaction $F_{(1,60)}$=8.62, *p*<0.01; [d]Group × Limb interaction $F_{(1,58)}$=21.43, *p*<0.0001; [e]Group × Limb interaction $F_{(1,60)}$=6.78, *p*<0.05

speculative and should be examined by means of functional neuroimaging.

Although previous research has found that encoding is more impaired than retrieval (Goodwin et al. 1969; Petersen 1977; Birnbaum et al. 1978; but see Fillmore et al. 1999), it is not clear in what phase of the BAC curve retrieval took place. Using a slowly rising BAC, our study showed alcohol effects also at retrieval, during the ascending limb. Limb of the BAC curve is thus an important dimension in delineating alcohol's amnesic effects. One explanation of impaired retrieval on the ascending but not descending limb is the development of acute tolerance with alcohol (cf. the Mellanby effect; Mellanby 1919; Moskowitz et al. 1979) on the descending limb. No such tolerance was observed at encoding, where the alcohol effect was more general and not re-

stricted to a particular limb. This could imply that the effect at encoding was of such strength that acute tolerance could not be developed. In a study on acute tolerance and motor performance, tolerance was more frequently developed in the group that received the lower out of two-alcohol doses (0.75 g/kg as compared to 1.0 g/kg; Bennett et al. 1993). Hence, improvement in performance on the descending limb as compared to the ascending limb likely occurs when sufficient mental resources are available due either to a relatively low BAC (e.g., 0.75 g/kg) or to a task or process that is relatively little impaired by alcohol (e.g., retrieval).

The neural correlates of differential behavior on the ascending and descending limbs have only been explored in a few studies. Using positron emission topography (PET), activation differences between the two limbs were found in right prefrontal cortex, anterior cingulate, and left superior temporal cortex (Schreckenberger et al. 2004). A reduced and delayed P300 in an auditory oddball paradigm during the ascending BAC was revealed by means of event-related potentials (ERPs; Lukas et al. 1990), possibly reflecting a disturbance of such functions as attention, memory updating, or information transfer to controlled processing and consciousness (Picton 1992). However, no clear comparison was made between the ascending and descending limbs in the aforementioned study (Lukas et al. 1990). Further exploration of cerebral activity and behavior during the two limbs should elucidate the differential effects on memory during the ascending and descending limbs of the BAC curve.

Alcohol's differential effect during the two limbs extended to mood. During the study session, the alcohol group scored higher on fatigue, depression, and confusion and lower on vigor on the descending limb than on the ascending limb, confirming earlier findings of negative mood during the descending limb (Babor et al. 1983; Earleywine and Martin 1993; Sutker et al. 1983). However, at test one week later, no mood difference between the ascending and descending limbs was found, although the alcohol group felt more tense, depressed, angry, and confused than the placebo group on the ascending limb at the high BAC. It is not clear why the mood response to alcohol would differ between the two sessions. The POMS is usually a reliable tool at longer time intervals when there is no intervention (Salinsky et al. 2001), but it is possible that having a second experimental session so close in time to the first made participants react differently to the alcohol during the second session.

Contrary to our expectations, in spite of specific retrieval cues being provided, cued recall was more impaired by alcohol than all other tasks, including free recall. This finding may be due to both free recall being reduced in both groups after the weeklong retention interval and to the elaborative processing of learning new semantic associations required in the cued recall task being impaired by alcohol. One of alcohol's effects is to reduce this kind of processing (Hashtroudi et al. 1984; Maylor et al. 1987), and deeper processing during intoxicated encoding does not benefit subsequent recall to the same extent as it does under sober conditions (Curran and Hildebrandt 1999; Hartley et al. 1978). The differential long-term effects of alcohol on the two tasks should be confirmed in future research.

The results from this study reveal the importance of the memory task itself in describing alcohol's effects on memory. For example, word-fragment completion (priming) was resistant to alcohol, replicating previous findings (Fillmore et al. 1999; Hashtroudi et al. 1984; Nilsson et al. 1989; Ray et al. 2004; Tracy and Bates 1999), whereas recognition of the completed fragments was significantly impaired by alcohol overall and by alcohol at encoding. Similarly, there were very different effects of alcohol on the two memory measures in the associative learning task. Recognition was sensitive to alcohol's detrimental effects on retrieval, particularly during ascending BAC. Cued recall, on the other hand, was sensitive to alcohol in general and to alcohol's detrimental effects on encoding. Although cross-task comparisons are limited to those tasks tested at similar BACs, very different results were thus obtained between and within tasks tested at the same BACs, demonstrating the selectivity of alcohol's effects on memory.

The weeklong retention interval used here limits comparison to previous research where the typical design has retrieval closely follow encoding on the same day. Although relevant for understanding the long-term effects of alcohol on memory and separating between alcohol effects on encoding and retrieval, the 1-week delay may have attenuated some of alcohol's effects due to forgetting in both groups. This possibility is supported by the results of the Parker et al. (1976) study that showed alcohol-induced retention decrement in immediate testing, but not 2 weeks later.

The exclusion of women in the present study also limits the findings to men. Apart from concerns of giving alcohol to women that may be undetectably pregnant, only men were selected to reduce variability of the data, inasmuch as it is known that cognitive skills can be affected differentially by alcohol in the two genders (e.g., Mumenthaler et al. 1999).

The mere expectation of alcohol frequently alters social behavior (Hull and Bond 1986; Marlatt and Rohsenow 1980) and has varying effects on cognitive and motor function. Such expectancy can improve performance by means of compensation (Marczinski and Fillmore 2005), but can also impair performance (Fillmore et al. 1998) or have no noticeable effect (Connors and Maisto 1980; Rimm et al. 1982; Nagoshi et al. 1992). Memory performance is usually unaffected by alcohol expectancy (Miller et al. 1978; Nelson et al. 1986; Assefi and Garry 2003), although memory was reduced as compared to controls following the ingestion of a placebo pill said to impair memory performance (Kvavilashvili and Ellis 1999). The absence in previous research of alcohol's expectancy effects on memory, and the successful placebo deception in the present study, caused us to limit our analyses to the direct effects of actual blood alcohol levels.

Although the current analyses were restricted to certain points of the BAC curve according to the question under investigation, using this type of paradigm also provides data tailored well to show the combined effects of having different BACs at encoding and retrieval and offer information on such topics as retrograde facilitation, state-dependent retrieval, and hangover effects for those wishing to explore these areas.

To summarize, the results of this study provide support for further investigation of alcohol's effects on human memory with reference to (1) distinguishing alcohol's effects on encoding vs retrieval, (2) limb of the BAC curve with particular attention to the ascending limb, (3) the nature of the memory probe, and (4) the critical interactions among these factors. These key findings may be useful in guiding future research on the neurobiological substrates of alcohol's effects on human memory.

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