Acute effects of alcohol on neural correlates of episodic memory encoding

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Although it is well established that alcohol impairs episodic memory encoding, it is unknown how this occurs on a cerebral level. We scanned intoxicated and sober individuals with functional magnetic resonance imaging (fMRI) while they encoded various materials that were recalled the following day. Alcohol impaired memory for object pairs and face–name pairs, but not for words and phrase–word pairs. Impaired performance was associated with reduced bilateral prefrontal activation and non-specific activation of the parahippocampal gyrus. These results suggest that alcohol impairs episodic memory by interfering with activity of regions involved in encoding, and further indicate which regions are critical for human memory.

Introduction

Alcohol is one of the world's most popular drugs, such that the subjective effects of alcohol on the mind and body are known to almost everyone. Thanks to a considerable amount of behavioral research, it is well established that alcohol impairs episodic memory as assessed through traditional laboratory memory tasks (Hashtroudi et al., 1984; Nilsson et al., 1989; Curran and Hildebrandt, 1999), and encoding more so than retrieval (Soderlund et al., 2005). However, even though this has been demonstrated behaviorally for decades, and in spite of advances in human neuroimaging techniques, no study has yet identified the neural correlates of alcohol-induced memory impairment. Identifying how alcohol interferes with episodic encoding is informative for both alcohol's effects on the brain, and for the neural correlates of episodic memory. Here we report the first study exploring alcohol's effects on brain activity during episodic memory encoding of verbal and nonverbal information.

There are many cerebral blood flow (CBF) studies of alcohol's effects on various processes, although no such study exists on episodic memory. Compared to placebo, alcohol reduces CBF in the task-implicated areas during perceptual processing, simulated driving (Calhoun et al., 2004), divided attention (Haier et al., 1999), and verbal fluency (Wendt and Risberg, 2001). This suggests that reduced CBF may also occur during memory processing. Hints about where such reductions may take place are found in the rodent literature, where mainly the hippocampus has been explored and identified as a target of alcohol's memory-impairing effects in a number of behavioral, in-vitro, and in-vivo studies (Silvers et al., 2003). Although it is possible that alcohol impairs memory in humans because of its effects on the hippocampus, it is likely that additional structures involved in memory, such as temporal structures surrounding the hippocampus (e.g., the parahippocampal gyrus) and the frontal lobes (Schacter and Wagner, 1999; Cabeza and Nyberg, 2000), also are affected by alcohol. Alcohol effects on both the parahippocampal gyrus and prefrontal cortex have been observed under acute intoxication (Schreckenberger et al., 2004). Our goal here was to determine which encoding-related brain areas have altered activity under the influence of alcohol, and to assess how these changes are related to subsequent memory performance.

Since this is, to our knowledge, the first study to assess the neural correlates of alcohol-induced memory impairment, we included tasks of varying difficulty and stimulus characteristics to cover a wide range of potential alcohol effects. Hence, the intention is not so much to compare alcohol's effects across tasks, but rather assess its effects within each task. Associative learning frequently activates the hippocampus (Henke et al., 1999; Sperling et al., 2003) and because of this area's suggested role in alcohol-induced memory impairment, we included associative learning of two types of materials: face–name pairs and pairs of line-drawings of objects, hereafter referred to as object pairs. Face–name pair encoding was used as it is impaired by the central nervous system depressants lorazepam and scopolamine (Sperling et al., 2002), and is relevant for real life situations. Lorazepam also impairs picture recognition (O'Neill et al., 1995), which motivated the inclusion of the object

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pairs. Unrelated object pairs were chosen, since processing of unrelated pairs is accompanied by more prefrontal activity than related pairs (Iidaka et al., 2001). Two verbal tasks were also included: a task of new semantic learning, consisting of witty word definitions (Tulving and Watkins, 1977), that has previously shown large effects of alcohol (Soderlund et al., 2005), and a word categorization task. These tests were included to examine alcohol's effect on the neural correlates of semantic processing, which has been associated with a reduction of left prefrontal activity (Wendt and Risberg, 2001).

We hypothesized that alcohol would impair subsequent memory performance in general, and associative memory in particular, because of the hippocampus' role in successful associative encoding and the previous reports of alcohol's influence on this region. Reduced performance was expected to be associated with reduced hippocampal activity during associative encoding, and with reduced left prefrontal activity during encoding in general.

Methods

Participants

Twenty-seven men were recruited for the study. Only men were chosen to reduce overall variability, given sex differences in the response to alcohol (Mumenthaler et al., 1999). They were screened over the phone prior to participation, and excluded if they had any neurological, psychiatric or medical disorder, were on any medication, were left-handed, had not spoken English regularly since the age of 7, were outside the 20–40 year age range, had problematic drinking habits or were unaccustomed to consuming alcohol (having less than two drinks per occasion, at least twice a month), were using marijuana on a regular basis, or had contraindications for fMRI (e.g., claustrophobia, metal objects inside the body). Participants reported consuming between 2 and 16 drinks a week, and no one had alcohol more than 3 times a week. All participants provided informed consent, approved by the Baycrest and Sunnybrook Research Ethics Boards. Participants were assigned to the placebo or alcohol condition (12 in each group; three participants were excluded due to excessive movement in the scanner or technical failure), matching groups for age (23.3±3.0 and 24.6±3.5, respectively), education (17.4±2.9 and 18.3±2.5), and initial memory performance (Rey's Auditory Verbal Learning Test List A (Rey, 1964); 6.8±1.7 and 7.8±1.5).

Materials

Four different episodic memory tasks were used, consisting of different materials: words, object pairs, face–name pairs, and phrase–word pairs. Since semantic processing enhances subsequent retrieval as compared to more shallow processing (Craik and Lockhart, 1972), participants were instructed to make semantic judgments about the materials to be remembered. They were also encouraged to memorize these materials for retrieval the following day. In addition to avoiding floor effects, the semantic manipulation encouraged participants to pay sufficient attention to the stimuli. A set of pilot tests was run to verify that materials were memorable the following day when alcohol had not been ingested. Since the different materials varied in memorability, their final list lengths differed. Using stimulus lists of 30–40 items depending on type of material, and presenting each stimulus twice provided

adequate levels of recall, while avoiding ceiling effects and keeping a margin for alcohol to have an effect.

Presentation order of the materials was counterbalanced across participants, and this order was the same at encoding and retrieval within a particular subject. Each type of material was presented in a separate scanning run, each of which consisted of the critical encoding condition requiring semantic processing (the "experimental/semantic condition"), and a "control/perceptual condition" which had highly similar stimuli but required only perceptual processing (see Fig. 1). In addition, the semantic condition for all materials but the words required associative encoding, which the perceptual condition did not. The word conditions contrasted words in the semantic condition to nonwords in the perceptual condition. Recall was only tested on the stimuli that had been encoded in the semantic conditions. Depending on the type of materials, the experimental part of each run was divided into six (all materials but the face–names) or eight blocks (face–names), and the control part was divided into five or seven blocks, respectively. The two types of blocks alternated, with each run starting and finishing with an experimental block. An instruction screen was presented at the beginning of each block for 3 s to remind participants of the requirements for the task to follow. A fixation base-line condition was obtained in the beginning and end of each run, where participants were asked to watch a cross-hair in the middle of the screen for 30 s. Retrieval of the materials seen in the scanner took place the following day in a purely behavioral session. A one-day delay was chosen for practical reasons, but it also meant that potential effects of alcohol on memory would be highly conservative since normal forgetting will occur regardless of alcohol.

Words

For the word experimental condition, nouns were presented, one at the time, in the middle of the screen for 2.5 s. There were 21 words in total (length: 5–10 letters; M: 7.4±1.1; frequency: 1–58; M: 10.7±15.1), and each word was presented twice across the six experimental blocks (24.5 s each). Between words, a cross-hair was presented for 1 s. Participants were asked to decide, for each of the nouns, whether it constituted something living or something non-living and to make a button press accordingly. For the control condition, pronounceable nonwords (e.g., thrabbed) of the same length drawn from the ARC Nonword Database (Rastle et al., 2002) were presented for 2.5 s each, each block lasting 14 s. Participants' task was to determine if the letter string contained the letter "a", and to press one of two buttons accordingly. Each of the six experimental blocks consisted of seven words, and each of the five control blocks consisted of four nonwords. The whole run lasted for 5 min and 14 s.

At retrieval, the 21 words were presented again in the middle of the screen, mixed with 21 new words of similar length and frequency (length: 5–19 letters; M: 7.3±1.0; frequency: 1–59; M: 11.0±15.8). The task was to say whether the presented word was recognized from the day before or not. Participants were allowed 10 s to answer, with the program moving forward as soon as they did. If a person said he recognized the word, he was immediately asked to make a remember/know judgment (Tulving, 1985; Gardiner, 1988) of his memory for this word and to press a button accordingly. Participants were instructed to answer "remember" if they clearly recalled seeing the word during encoding, possibly recalling something they thought or felt when seeing the word. They answered "know" if the word did not evoke such a feeling,

Fig. 1. Memory tasks. Materials presented in the semantic and perceptual conditions in the scanner on Day 1, and at retrieval on Day 2. (A) Words. (B) Phrase-word pairs. (C) Object pairs. (D) Face–name pairs. Presentation order of the different materials was counterbalanced across participants, with each material type (e.g., words) corresponding to a run. The semantic and perceptual conditions were interleaved in blocks, with each run starting end ending with a semantic block. Materials were retrieved in the same order in which they were encoded the previous day.

but they simply knew that they had seen the word the previous day. A comparison was given to when you recognize someone in the street, where recalling where you know the person from corresponds to "remember", and knowing that you know the person but not from where corresponds to a "know" response. This paradigm was included to examine effects of alcohol on the quality of the subsequent memory experience.

Object pairs

Eighteen pairs of line drawings of objects (Snodgrass and Vanderwart, 1980) were presented in the experimental condition, with each pair being presented twice, and each block containing six pairs. Each stimulus was presented for 4 s, followed by a cross-hair presented for 1 s, resulting in 30 s blocks. For each object pair, participants were asked to decide if there was a meaningful relationship between the objects, and to press a button accordingly. Semantically unrelated pairs were chosen since earlier studies have found that they give rise to more prefrontal activity than related pairs (Iidaka et al., 2001). Unrelated pairs would also make participants think more thoroughly about the stimuli than had they been related, and encoding should thereby be enhanced. The stimuli for the control condition were two identical objects presented together, with one of them being smaller than the other. Participants' task was to indicate whether the smaller object was to the right or to the left, by pressing the corresponding button. Control stimuli were presented under identical conditions as the semantic stimuli, except there were 5 blocks, 3 pairs per block. Each control block was 15 s long, and the whole run lasted for 5 min 55 s.

At retrieval, the same line drawings were shown again, but half the pairs had been rearranged into new combinations. In rearranged pairs, a given drawing was always shown in the same position (left or right) so that the only thing changing between encoding and retrieval was the association between the two objects rather than their location on the screen. Participants' task was to say whether the presented objects were in the same or a different combination as compared to the day before. Each pair was presented on the screen for 10 s, or until the person had given an answer.

Face–name pairs

In the experimental condition, participants were shown photos of people with a gender-appropriate name under them (Naveh-Benjamin et al., 2004), and were asked to judge whether the name fit the face or not. The 20 pairs (half of older people, half younger people, half men, half women), five per block, were each shown twice for 4 s per pair, followed by a 1 s cross-hair. Each block lasted 25 s, and participants pressed one of two buttons according to their judgment. In the control condition, photos of people were shown without a name under them. Instead it said either "Man" or "Woman" (Herholz et al., 2001), which was a correct description of the person in the picture on half of the trials, and an incorrect description on half the trials. The participant's task was to say whether the label was correct or not, and to press a button accordingly. Presentation conditions were the same as for the experimental stimuli, except there were 3 pairs per block, seven blocks, and each block lasting 15 s. The run took 6 min and 55 s.

The following day at retrieval, memory was assessed in three steps: forced choice name recognition, face recognition, and face–name pair recognition. In the name and face recognition tasks, a stimulus from the previous day was presented with a new stimulus, and participants were asked to indicate which of the two stimuli was seen the day before by means of a button press. In the face–name recognition task, either a face or a name from the day before was presented with either two names or two faces—one of which had been presented the previous day. Participants' task was to

indicate with a button press which name (or face) had been presented with that face (or name) the previous day. Each stimulus was presented on the screen for 15 s, or until the person had given an answer.

Phrase-word pairs

A fourth kind of material was used, which consisted of a short sentence followed by a word (e.g., a study of the outer layer—DERMATOLOGY) (Tulving and Watkins, 1977). The brief sentence was a more or less witty definition of the word, and participants' task was to indicate with a button press whether they indeed found the definition clever or not. Each of the 30 phrase–word pairs was presented once for 4 s, 5 pairs per block, and between each pair, a cross-hair was presented for 1 s. Each experimental block lasted 25 s. The control stimuli consisted of similar sentences, written in upper or lower case, but without the word following the sentence. Participants were asked to indicate through a button press whether the sentence was written in upper or lower case. There were 5 control blocks with 3 stimuli per block, each block taking 15 s. The whole scan lasted for 5 min and 22 s.

At retrieval, participants were shown the 30 experimental phrases, one at a time, and were asked to say which word they defined. If they did not remember, they were encouraged to guess. Time was unlimited, but when they could not think of anything the experimenter continued to the next phrase. Participants answered out loud, and the answers were recorded by the experimenter.

Procedure

Participants were seen on 2 days. Upon arrival at the laboratory the first day, they signed an informed consent form and gave an initial breath sample to ensure sobriety. They were thereafter asked questions regarding compliance with instructions (e.g., not having had any alcohol the last 24 h, not having eaten anything the last 4 h), how much they slept the night before, and were weighed. A brief memory test (Rey's Auditory Verbal Learning Test; Rey, 1964) was administered, and participants were thereafter familiarized with the tasks to be performed in the scanner. After a few practice trials of the different tasks, participants were given their first drink that had been prepared by the experimenter in a separate area. They were instructed to drink it progressively throughout 15 min, and were thereafter given a second drink, also to be consumed in 15 min. Upon finishing the drinks, participants gargled thoroughly and thereafter provided a pre-scan breath sample. They were then placed in the scanner, in which they remained for about an hour. Immediately after scanning, participants gave a post-scan breath sample, and were asked to estimate how long they had been in the scanner, how much they had had to drink, and were given a questionnaire about their alcohol habits (AUDIT; Saunders et al., 1993). They were then released, and those who had been in the alcohol group were put in a taxi and sent home. All participants came back the following day to test their memory for the materials presented in the semantic condition in the scanner. There was no beverage or scanning this second day.

Alcohol administration

The alcohol group was given 0.8 g/kg alcohol, distributed in two drinks made up of one part 95% ethanol and seven parts orange juice. This dose corresponds to a little less than a bottle of wine for a man of 80 kg, and made participants feel rather intoxicated. Participants had 15 min to consume each drink. The placebo group was given 0.05 g/kg alcohol, a dose too small to

have any observable effect, distributed under the same conditions. The amount of orange juice was the same had they received the higher dose, and the plastic cup and the surface of the drink were sprayed with an ethanol–water mix to give olfactory cues of alcohol.

Blood alcohol concentration (BAC) readings

Participants' BAC levels were assessed from breath samples using the Alert J4X.ec analyzer (Alcohol Countermeasure Systems, Toronto, ON). A back-up breathalyzer (S-D2, CMI, Inc., Owensboro, KY, USA) was used once when the standard one failed. Measurements were made upon arrival, before entering the scanner, and after participants came out of the scanner. All participants were sober upon arrival, and mean BACs before and after scanning were 0.69 ± 0.24 and 0.65 ± 0.10 mg/dl, respectively.

fMRI scanning and analyses

Scanning was performed at Sunnybrook and Women's College Health Sciences Centre on a research-dedicated whole-body 3.0 T MRI system (Signa 3T94 hardware, VH3M3 software; General Electric Healthcare, Waukesha, WI) with a standard quadrature bird-cage head coil. Participants were placed in the scanner in supine position, with their head firmly placed in a vacuum pillow to minimize head movement. Earplugs were provided to reduce the noise from the scanner, and sensors were placed on participants' right index finger and around the chest, to monitor heart rate and respiration. A volumetric anatomical MRI was performed before functional scanning, using standard high-resolution 3D T1-weighted fast spoiled gradient echo (FSPGR) images (TR/TE=7.2/3.1 ms, inversion-recovery prepared T1=300 ms, flip angle 15°, 256×192 acquisition matrix, 124 axial slices 1.4 mm thick, voxel size=0.86×0.86 cm, FOV=22×16.5 cm). Functional imaging was performed to measure the blood oxygenation level-dependent (BOLD) effect (Ogawa et al., 1990). Scans were obtained using a single-shot T2*-weighted pulse with spiral in-out, achieving 28 slices, each 5 mm thick (TR/TE=2000/30 ms, flip angle 70°, 64×64 acquisition matrix, 28 axial slices 5 mm thick, voxel size=3.125×3.125, slice spacing=0, FOV=20×20 cm).

Data processing and analyses were performed using Analysis of Functional NeuroImages software (AFNI; Cox and Hyde, 1997), analyzing the four types of materials separately. The initial five time points from each image volume were removed from analyses to allow for the brain magnetization to stabilize. Time-series data were spatially co-registered (aligned volumetrically to a reference image within the run, using the 3dvolreg program in AFNI) to correct for small head motion using a 3-D Fourier transform interpolation, and the linear trends were removed. Uncorrected head motion (spikes) was identified through visual inspection and reduced through averaging the two surrounding time points. Physiological motion (respiration and heart beat) was also removed through linear filtering. The data were normalized temporally and thereafter deconvolved, using the AFNI plugin 3dDeconvolve.

T-statistics contrasting semantic and perceptual processing to a fixation baseline were calculated for each participant and each material type to create statistical maps. A general linear model was used to model the data. We constrained the shape of the hemodynamic response function by convolving the stimulus time-series with a gamma function to obtain ideal waveform time-series that later were used in the individual analysis. These activation maps were then transformed into stereotaxic space

(Talairach and Tournoux, 1988; Cox and Hyde, 1997), by first aligning the anterior–posterior-commissure and inferior–superior axes of the structural scans, scaling them to fit the Talairach–Tournoux Atlas brain. Activation maps were spatially smoothed with a Gaussian filter with a full width at half maximum value of 6.0 mm to minimize individual variation of the anatomical landmarks. These steps were performed to facilitate the subsequent group analysis, which consisted of voxelwise, mixed effects (groups fixed, conditions fixed, participants random), three-factor ANOVAs, one for each type of material, with group as a between-subject factor and condition (semantic and perceptual) as a within-subject factor. We only report group×condition interactions significant at $p<0.005$, with clusters being >150 µl (about 3 voxels), and having a connectivity radius of 2 mm (i.e., two clusters need to be separated by at least 2 mm to be considered different). In addition, the BOLD response had to be significant within at least one of the two groups at $p<0.005$. This gives a joint probability threshold of $p<0.00003$ (cf. Allan et al., 2000; Cabeza et al., 2004). For example, a voxel coordinate reflecting an apparent difference between placebo and alcohol groups had to meet the additional criterion that the same brain coordinate's BOLD signal was significantly different in the semantic condition relative to the perceptual condition in at least one of these groups.

Conjunction analysis (Friston et al., 1999) was used to assess activations occurring in the semantic vs. perceptual contrast in the placebo group for all materials to identify material-independent encoding areas. The voxels entering into this contrast had to be significant at $p<0.005$, and the criteria for an overlap were a cluster of at least 50 µl.

Placebo deception

Even though all participants accurately guessed which group they had been assigned to at the end of the experiment, the placebo group believed they had received more alcohol than they actually had (2.1 ± 0.9 drinks). This figure was significantly higher in the alcohol group (4.7 ± 1.5; $t_{22}=-5.1$, $p<0.0001$).

Results

Behavioral data (Day 1)

There was no difference between the groups in reaction time or responses in the scanner on Day 1. These data can be viewed in Supplementary Table 1.

Memory performance (Day 2)

Performance in word recognition ($F<1$), cued recall ($F<1$), and face recognition ($F_{1,23}=3.0$, $p>0.05$) was equivalent in the two groups (Table 1). In addition to word recognition, we also assessed the quality of the memory experience using the remember/know paradigm (Tulving, 1985; Gardiner, 1988), where a "remember" response indicates that a participant can recall some specific aspect of the encoding of the stimulus in question. Although there were no differences between groups in word recognition, the alcohol group gave fewer "remember" responses than the placebo group did to qualify their word recognition. In addition, the alcohol group performed worse than the placebo group in recognition of object pairs ($F_{1,23}=9.5$, $p<0.01$), face–name pairs ($F_{1,23}=5.8$, $p<0.05$), and the names presented with the faces ($F_{1,23}=4.8$, $p<0.05$; see Table 1).

Table 1
Recall performance on Day 2: mean proportions (SD)

	Placebo	Alcohol	F
Words (Rn)	0.82 (0.06)	0.84 (0.05)	0.5
"Remember" responses	0.78 (0.15)	0.63 (0.15)	5.8 *
Phrase-word pairs (cued Rc)	0.47 (0.19)	0.42 (0.14)	0.6
Object pairs (ass. Rn)	0.77 (0.10)	0.63 (0.12) **	9.5**
Face–name pairs			
Faces (Rn)	0.83 (0.21)	0.69 (0.21)	3.0
Names (Rn)	0.86 (0.12)	0.69 (0.23)	4.8*
Face–name pairs (ass. Rn)	0.61 (0.16)	0.46 (0.16)	5.8*

Rn=recognition; Rc=recall; ass.=associative; n.a.=not applicable.
* $p<0.05$.
** $p<0.01$.

Functional neuroimaging data (Day 1)

To examine brain activity during the semantic encoding conditions, and the effects of alcohol on this activity, we contrasted the fMRI images obtained during the semantic conditions to those obtained during the perceptual conditions within each group, and then group differences in this contrast were assessed. The term "activation" will hereafter refer to a significantly *larger* BOLD signal in the semantic as compared to the perceptual condition, and "deactivation" to a significantly *smaller* BOLD signal in the semantic as compared to the perceptual condition. Differences in activation/deactivation between the two groups in association with a difference in performance would suggest that the area in question is a target for alcohol-induced encoding impairment.

Consistent with the equivalent performance of the two groups on the word tasks, both activated areas in the left inferior prefrontal gyrus during encoding of words and phrase–word pairs (Fig. 2, Tables 2 and 3). However, there also were differences in the BOLD response between the groups during encoding of words, despite their similar recall performance. The placebo group activated additional areas in the left inferior frontal gyrus, more superior to those active in both groups, as well as regions in the right superior and middle frontal gyri and right superior temporal gyrus. None of these regions was active in the alcohol group. Other significant group differences were seen in regions where there was a deactivation during semantic encoding in the alcohol group, and no change of activity in the placebo group. These were seen mainly in posterior structures, including the precuneus, lingual gyrus, and cerebellum.

During associative object encoding, compared to perceptual encoding, the only region that was active in both groups was an area in the left superior frontal gyrus, likely the supplementary motor cortex (Table 4). In contrast, a number of regions differentiated the alcohol group from the placebo group. There was a large right-sided (middle) frontal activation in the placebo group (see Fig. 2), as well as posterior activations including the right cerebellum, the bilateral parahippocampal gyrus, the left lateral occipital complex, the left precuneus, and a number of extrastriate areas in both hemispheres. None of these regions was significantly active in the alcohol group. A number of deactivations were also observed in the placebo group (left precentral gyrus, right paracentral lobule and superior temporal gyrus, and left cingulate regions) that were not present in the alcohol group. On the other hand, the alcohol group activated the left medial frontal gyrus, an area that was inactive in the placebo group. Finally, for face–name encoding, there were no areas that were activated in
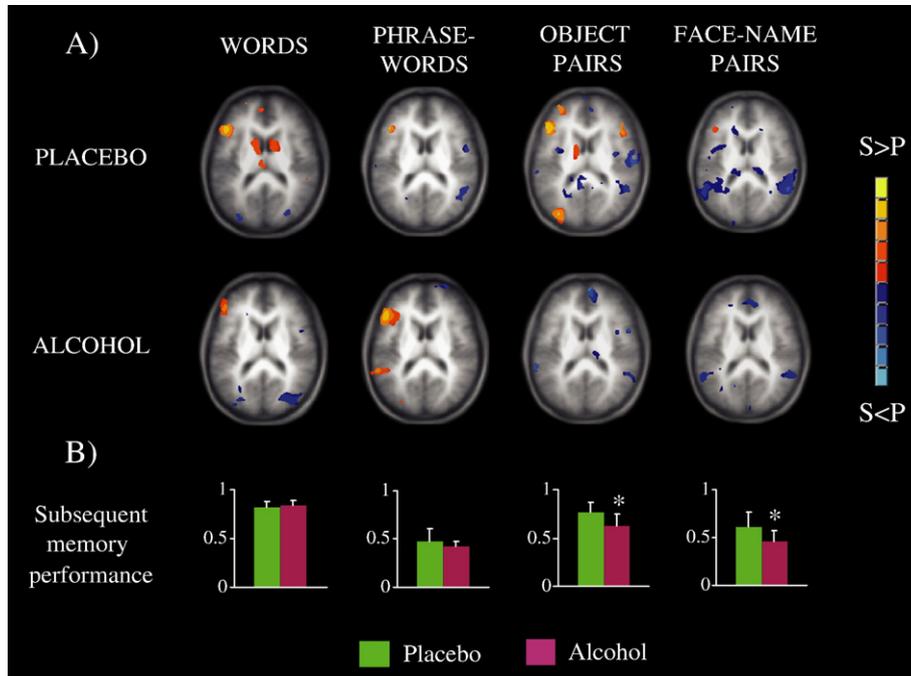
Fig. 2. Brain activity and memory performance. (A) Activations in the placebo and alcohol groups during encoding of different materials on axial slices at *z*: 15. Warmer colors represent semantic > perceptual, and cooler colors represent perceptual > semantic. S = semantic condition; P = perceptual condition. Notice the left inferior prefrontal activation in the placebo group throughout all tasks. This area was also activated in the alcohol group during encoding of verbal materials, for which retrieval was intact. The alcohol group did not activate this area during encoding of non-verbal materials, for which retrieval was impaired. (B) Recall performance in the two groups the day following encoding. The alcohol group's performance in word recognition and cued recall of words was similar to the placebo group's, but they were impaired on object pair and face–name pair recognition.

both groups. The main difference between the groups during face–name encoding was a right-sided (inferior) frontal activation in the placebo group, not present in the alcohol group. The left precuneus and right temporal regions were deactivated in the placebo group but inactive in the alcohol group.

To ensure that all activations during the semantic conditions were true activations above baseline, and not due to deactivations in the perceptual condition, we inspected the BOLD responses of the semantic and perceptual conditions vs. fixation separately. This analysis was particularly informative regarding the medial temporal
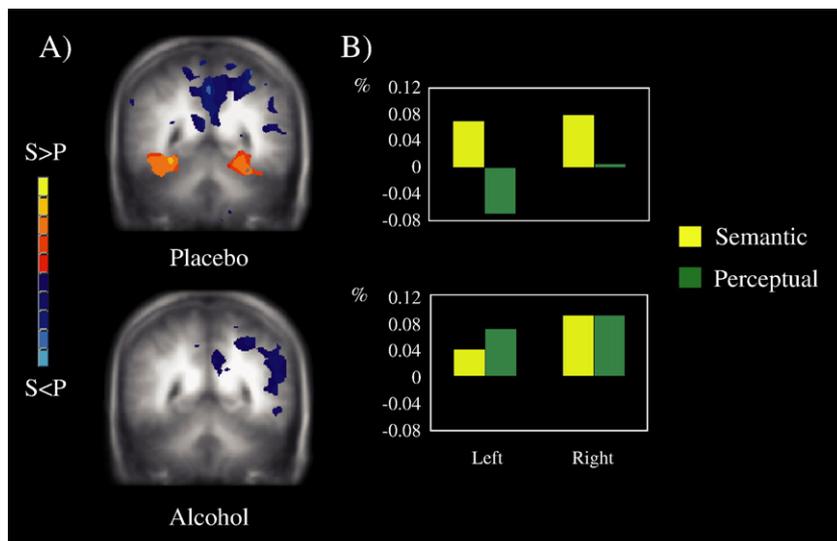

Fig. 3. Non-selective parahippocampal/fusiform activation in the alcohol group. (A) Activity in the parahippocampal/fusiform gyrus in the placebo group and lack of parahippocampal activation in the alcohol group during semantic object pair encoding compared to perceptual encoding. (B) Percent change in the BOLD signal of the parahippocampal/fusiform gyrus for each condition vs. fixation for the two groups. The apparent lack of activation in the alcohol group was due to increased activity in this structure during both the semantic and the perceptual condition compared to fixation. The placebo group only activated this structure during the semantic condition. Left and right refer to the left and right parahippocampal/fusiform gyri, and % refers to % BOLD change as compared to fixation.

Table 2
BOLD signal coordinates in the placebo and alcohol groups during word encoding

Region	Cluster size; μl	BA	X	Y	Z	F	Placebo (t)	Alcohol (t)
Alcohol = Placebo								
L inf fro gyr	1034	47	−44	26	3		6.3	3.8
L med fro gyr	605	8	−9	43	42		6.5	3.2
L sup fro gyr	529	8	−5	19	52		4.5	4.1
L middle fro	180	6	−34	10	46		4.3	4.3
Alcohol ≠ Placebo								
L inf fro gyr	775	45	−48	23	18	20.5	8.0	1.2
R sup temp gyr	596	22	48	−34	3	18.8	5.8	−1.6
R middle fro gyr	505	47	37	42	−4	21.1	5.4	−0.6
R sup fro gyr	368	6	3	14	60	14.6	5.7	−0.6
L culmen	6074	−	−35	−52	−22	17.6	1.5	−5.3
L precuneus	2601	7	−1	−62	56	21.0	−2.9	−7.2
L lingual gyr	1453	18	−25	−90	−6	27.2	−1.3	−7.0
L cing gyr	666	24	−19	−8	29	17.7	−0.3	−5.0
L inf par lobule	407	40	−42	−32	30	15.2	−0.2	−6.8
R culmen	1204	−	23	−42	−24	20.9	2.9	−3.5
R cuneus	679	19	13	−91	34	14.1	1.1	−3.7
L inf fro gyr	362	47	−44	22	−2	24.1	11.0	4.3

Notes. BA = Brodmann area (BA). Coordinates are in standardized space of Talairach and Tournoux (1988). *F* values are shown for the group × condition interaction ($p < .005$), and the placebo and alcohol group *t*-values refer to the semantic vs. perceptual comparison within each group. *T*-values > 3.6 are significant at $p < .005$. Similarities between groups (=) were assessed through conjunction analysis, and differences (≠) through ANOVA group × condition interactions. 1 voxel ≈ 48 μl.
L = left; R = right; inf = inferior; fro = frontal; gyr = gyrus; med = medial; sup = superior; temp = temporal; cing = cingulate; par = parietal.

lobes. It revealed that the apparent lack of bilateral parahippocampal activation in the alcohol group during semantic object encoding was due to activation in both the semantic and perceptual conditions. As can be seen in Fig. 3, the placebo group activated this structure during the semantic condition, but had reduced activity (left) or no change in activity (right) in the parahippocampal gyrus during the perceptual condition. The alcohol group, on the other hand, activated it to a similar degree in both conditions.

Hippocampal activation was expected but not found in the placebo group during object pair and face–name pair encoding. Because the hippocampus is more activated by new stimuli than repeated ones (Tulving et al., 1996; Dolan and Fletcher, 1997), and our stimuli were presented twice, we reanalyzed the BOLD responses including only the first presentation of each stimulus, but still found no hippocampal activation. The BOLD response in the two conditions (semantic and perceptual vs. fixation) was also examined separately. For object pairs, the placebo group deactivated the left hippocampus in both conditions but activated the right during the perceptual condition (see Supplementary Table 2). The alcohol group on the other hand deactivated the hippocampus bilaterally during both conditions. While processing the face–names, the placebo group activated the right hippocampus and deactivated the left in both conditions, whereas the alcohol group showed the opposite pattern (see Supplementary Table 2). In summary, the pattern of hippocampal activity was not consistent in either group, and since the hippocampus was often active in both conditions, this region did not appear as significantly activated when the two encoding conditions were contrasted.

Table 3
BOLD signal coordinates in the placebo and alcohol groups during phrase–word pair encoding

Region	Cluster size; μl	BA	X	Y	Z	F	Placebo (t)	Alcohol (t)
Alcohol = Placebo								
L inf fro gyr	3159	45	−40	26	5		3.8	4.2
L fusiform gyr	563	19	−36	−72	−13		4.1	4.2
L precentral/middle fro gyr	440	6	−39	−0	41		4.0	3.9
L sup fro gyr	274	6	−5	14	52		3.8	4.2
Alcohol ≠ Placebo								
L inf par lobule	2774	40	−42	−50	58	17.1	−4.9	−2.5
R precuneus	1428	7	8	−49	45	15.8	−5.6	0.5
R inf par lobule	193	40	41	−40	25	14.7	−5.4	0.3

Notes. BA = Brodmann area (BA). Coordinates are in standardized space of Talairach and Tournoux (1988). *F* values are shown for the group × condition interaction ($p < .005$), and the placebo and alcohol group *t*-values refer to the semantic vs. perceptual comparison within each group. *T*-values > 3.6 are significant at $p < .005$. Similarities between groups (=) were assessed through conjunction analysis, and differences (≠) through ANOVA group × condition interactions. 1 voxel ≈ 48 μl.
L = left; R = right; inf = inferior; fro = frontal; gyr = gyrus; sup = superior; par = parietal.

Table 4
BOLD signal coordinates in the placebo and alcohol groups during object pair encoding

Region	Cluster size; µl	BA	X	Y	Z	F	Placebo (t)	Alcohol (t)
Alcohol = Placebo								
L sup fro gyr	232	6	−5	8	55		6.3	4.3
Alcohol ≠ Placebo								
R middle fro gyr	2630	46	43	33	15	20.2	3.7	−2.6
R culmen	212		36	−43	−21	13.3	5.4	−0.6
L fusiform/parahippo	202	37	−36	−46	−9	13.7	7.0	2.3
R parahippo	191	37	29	−46	−7	12.3	5.2	0.02
L precuneus	270		−29	−60	35	11.0	5.3	0.8
L middle occip gyr	689	19	−54	−65	−4	16.8	5.9	0.5
L lingual gyr	166	18	−29	−71	−7	12.0	4.5	0.5
R lingual gyr	518	17	14	−92	−6	14.1	4.6	−0.7
R sup temp	299	22	53	7	−2	11.8	−3.8	0.02
L precentral gyr	724	6	−45	−7	29	26.2	−4.4	2.7
L cing gyr	222	31	−18	−24	41	13.9	−3.9	0.9
R paracentral lobule	400	31	8	−29	43	10.7	−5.6	−1.7
L post cing	190	29	−2	−38	19	11.5	−6.1	0.9
L med fro	321	6	−15	5	48	21.1	−2.5	3.8

Notes. BA=Brodmann area (BA). Coordinates are in standardized space of Talairach and Tournoux (1988). *F* values are shown for the group×condition interaction ($p < .005$), and the placebo and alcohol group *t*-values refer to the semantic vs. perceptual comparison within each group. *T*-values > 3.6 are significant at $p < .005$. Similarities between groups (=) were assessed through conjunction analysis, and differences (≠) through ANOVA group×condition interactions. 1 voxel ≈ 48 µl.
L=left; R=right; sup=superior; fro=frontal; gyr=gyrus; parahippo=parahippocampal; occip=occipital; temp=temporal; cing=cingulate.

Finally, to identify regions underlying semantic encoding regardless of type of material, we performed a conjunction analysis to assess activations that were present in all semantic encoding conditions in the placebo group. Such activation was found in a region in the left inferior/middle frontal gyrus (−42; 28; 15, $p < .005$; 114 µl, see Fig. 2). As can be seen in Fig. 2, the alcohol group also had left prefrontal activation during encoding of verbal materials where their performance was intact, but they had no such activation during encoding of the pictorial materials where their performance was impaired. To test if this difference was statistically significant, we defined this area as a region of interest (using the area identified in the conjunction analysis of the placebo group), extracted the mean BOLD signal from this region in all subjects in the two conditions vs. fixation, and then calculated the difference in signal between the perceptual and semantic conditions. Two 2 (Materials)×2 (Group) repeated measure ANOVAs were run on these values, including the words and cues in one, and the objects and face–name pairs in the other. In this way, we were able to examine the encoding activity for those materials that were remembered well by the alcohol group separately from activity associated with those that were poorly remembered. There was no overall effect of group or interaction of group and materials in the words/cues ANOVA ($ps > .10$). However, there was an effect of group in the objects/face–names ANOVA ($F_{1,22} = 5.5$; $p < .05$) due to the fact that activity in the semantic condition was significantly smaller in the alcohol group than in the placebo group for both these materials (see Fig. 2 and Supplementary Table 3).

Discussion

This is the first study to identify some of the neural correlates of alcohol-induced memory impairment in humans during episodic encoding of various materials. Three major findings emerged. First,

when performance was spared under alcohol, i.e., for verbal materials, the alcohol group activated the same set of left prefrontal regions at encoding, including the inferior frontal gyrus, as the placebo group. The left inferior frontal gyrus was not active in the alcohol group during encoding when subsequent memory performance was impaired, i.e., for non-verbal materials. Second, encoding under the influence of alcohol also was associated with reduced activity in other encoding-related areas, such as the right middle frontal gyrus (objects), right inferior frontal gyrus (face–names), and the parahippocampal and fusiform gyri (objects). Third, the apparent lack of parahippocampal/fusiform activity under impaired encoding was in fact due to non-specific activation during both the experimental condition and the control condition in the alcohol group.

The first finding was that there was a common area of activation in the two groups during encoding of materials that were later equally recalled (words and phrase–word pairs), in the left inferior prefrontal cortex (BA 46). This area was active in the placebo group throughout all tasks, but in the alcohol group only in tasks where subsequent recall was intact. In accordance with this finding, this area has been associated with successful encoding of face–name pairs and words (Wagner et al., 1998; Sperling et al., 2003), encoding of objects, words and faces (Kapur et al., 1996; Kelley et al., 1998), and semantic processing of verbal and nonverbal material (Kapur et al., 1994; Vandenberghe et al., 1996).

A legitimate question is why the alcohol group was able to activate this area during certain tasks, but not during others. For the word materials, it is plausible that the living/non-living judgment task was so well-defined in terms of right and wrong answers that no particular strategy to solve the task was needed, and the crucial area for subsequent recall was activated without much self-initiation. It should be noted here, however, that the left inferior prefrontal activation in the alcohol group was less

robust than that in the placebo group. This may be related to the alcohol giving fewer "remember" responses to qualify their subsequent recognition, in spite of equivalent recognition scores. Although there were no right and wrong answers in the word-phrase task, it is quite straightforward to judge whether something is clever or not and it can be done simply through personal preference. This probably induced the activation in a semi-automatic fashion like that for words alone. In contrast, the object and face–name tasks, where subsequent memory performance was impaired by alcohol, required the participants to set the criteria for their judgments. For example, a table and a giraffe could be considered having no association based on animacy, but having an association based on the common four legs. This open structure may have made it harder for the alcohol group to activate areas crucial for remembering.

Our second finding was that the alcohol group failed to show the right prefrontal activation during encoding of objects and faces/face–name pairs that was seen in the placebo group. The placebo group activations are in line with previous research reporting right prefrontal activation for the encoding of nonverbal materials (Kelley et al., 1998) including associative encoding (Klingberg and Roland, 1998). Importantly, activity in right prefrontal cortex also is increased during the encoding of nonverbal items that later are remembered compared to those that are forgotten (Brewer et al., 1998). Hence, our finding of reduced activation of right prefrontal cortex in the alcohol group (right middle frontal for objects and inferior frontal for face–names) during non-verbal encoding is consistent with their subsequently impaired memory for these stimuli. A larger impairment of right than left hemispheric functions has been shown with similar or higher doses of alcohol, impairing shape-search in the left visual field (right hemisphere) but not impairing verbal or right visual field search tasks (Chandler and Parsons, 1977). Neurophysiologically, some of alcohol's largest effects, as assessed by evoked potentials, are in the right prefrontal cortex (Kahkonen et al., 2003). This work, taken together with our results, suggests that right prefrontal cortex may be particularly vulnerable to the effects of alcohol, perhaps via reduced excitability, which in turn has particularly adverse effects on memory for nonverbal material.

The third novel finding of this study was a differential bilateral activation of the parahippocampal and fusiform gyri in the placebo group during object pair encoding, in line with previous research on object pairs (Kelley et al., 1998; Iidaka et al., 2001), pictures (Stern et al., 1996; Wagner et al., 1998), and successful encoding of objects (Garoff et al., 2005). The alcohol group was markedly impaired in recalling these materials, and at a first glance did not show any parahippocampal activity during semantic compared to perceptual encoding. However, this apparent lack of activation was due to increased activity, vs. fixation, in both the semantic and perceptual conditions. This non-specific activation during both kinds of processing can be compared to older individuals activating striate cortex during both a lexical task and a perceptual baseline task, as compared to younger participants who only showed increased activity during the lexical task (Madden et al., 2002). This type of non-selective activation may have been due to the perceptual task being more demanding for the intoxicated (or older) individuals requiring additional neural recruitment to achieve a similar level of performance. It may also be that alcohol leads to less flexible cognitive networks, such that they get "locked" into a certain configuration due to the prior occurrence of a high-demanding block. Because we used a block-design with interleaved semantic and perceptual blocks, it is possible that the alcohol group was unable to modulate activity in the parahippocampus appropriately to reflect the change in task demands. Such non-specific activation during encoding may lead to worse performance during recognition since areas active during encoding often are reactivated during recognition (Daselaar et al., 2004). If there was no neural "signature" that was specific to a particular stimulus at encoding, there could be no support from such a signature during recognition to guide the response. Finally, a non-specific activation across tasks may result from disrupted inhibition during the lower-level task. The primate literature has revealed an array of parahippocampal afferents (Suzuki and Amaral, 1994) that may modulate the activation in this region. Alcohol's effect on a certain structure may hence not only be direct, but also may be mediated through its effect on afferents to this structure, such as BA 46 in the frontal lobes (Suzuki and Amaral, 1994).

Some of the effects of alcohol on brain activity may occur without an adverse impact on encoding. For example, in object pair and face–name pair encoding, there were additional areas where activity differentiated the groups (see Tables 2–5), such as areas of extrastriate cortex. However, previous research suggests that the areas discussed above, namely the (right) prefrontal cortex and the parahippocampal gyrus, are important components of the encoding network. That is, activation of these structures is positively associated with subsequent memory for unrelated object pairs (Iidaka et al., 2001) and complex pictures (Brewer et al., 1998), so their deficient activation in the alcohol group may be the prime mechanism underlying this group's ineffective encoding.

In addition to reduced activation in those encoding conditions associated with impaired subsequent memory, differences also were

Table 5
BOLD signal coordinates in the placebo and alcohol groups during face–name pair encoding

Region	Cluster size; μl	BA	X	Y	Z	F	Placebo (t)	Alcohol (t)
Alcohol ≠ Placebo								
R inf fro gyr	2630	47	48	16	−5	21.5	4.1	−2.3
L precuneus	1708	7	0	−42	43	17.5	−8.1	−2.9
R insula/sup temp gyr	640	22	56	−34	18	21.7	−7.6	−0.7
R sup temp	179	22	46	−44	19	10.6	−6.4	−2.8

Notes. BA = Brodmann area (BA). Coordinates are in standardized space of Talairach and Tournoux (1988). *F* values are shown for the group × condition interaction ($p < .005$), and the placebo and alcohol group *t*-values refer to the semantic vs. perceptual comparison within each group. *T*-values > 3.6 are significant at $p < .005$. Similarities between groups (=) were assessed through conjunction analysis, and differences (≠) through ANOVA group × condition interactions. 1 voxel ≈ 48 μl.
L = left; R = right; inf = inferior; fro = frontal; gyr = gyrus; sup = superior; temp = temporal.

seen in patterns of deactivation (i.e., less activity during the semantic condition compared to the perceptual condition). The placebo group deactivated a number of regions not deactivated by the alcohol group. These included the left cingulate, precentral gyrus, and the right paracentral lobule and superior temporal gyrus. Some of these regions (posterior cingulate and other medial regions) are often deactivated during cognitively challenging tasks, compared to low level baselines, leading to the suggestion that they form the brain's "default mode" network (Raichle et al., 2001). The term "default mode" refers to the state of alert monitoring of the internal and external milieus that participants engage in when not required to carry out a specific cognitive task. Our finding of reduced deactivations in these areas indicates that alcohol may not only alter task-related activations of the brain, but also, directly or indirectly through altered inhibition, may alter the ability to modulate default mode activity. Such a failure to suppress activity in these default mode structures has been observed in older individuals (Grady et al., 2006) and after sleep deprivation in young adults (Chee and Choo, 2004), suggesting that the default mode network may be sensitive to a variety of perturbations, including the effects of alcohol consumption. In contrast to the nonverbal conditions, during the word task, where performance was intact, the alcohol group deactivated a number of regions not deactivated in the placebo group. Among these deactivated regions were the cerebellum, which frequently shows reduced CBF during intoxicated rest (Volkow et al., 1988), and the precuneus and cingulate gyrus. Greater deactivations of these default mode regions may indicate that the alcohol group experienced the task as harder and therefore suspended activity to a greater extent compared to the placebo group.

Hippocampal activation was expected but not found in the associative encoding tasks in this study, i.e., the object pair and the face–name pair tasks. This lack of activation occurred because the hippocampus was also active in the perceptual condition to which the associative condition was compared. The increased activity of the hippocampus during the lower level perceptual task could be because this condition also contained new materials. This is consistent with the idea that the hippocampus is more activated by novelty than association, as has been suggested by others (Dolan and Fletcher, 1997).

This is the first study assessing the neural correlates of alcohol's memory-impairing effects, and as such it is of an exploratory nature. A confound was that the two tasks that were affected by alcohol contained both a non-verbal and an associative component. It is thus not clear whether the neural correlates of alcohol-induced impairment reported here represent impaired encoding of a particular type of material (non-verbal), impairment of a particular type of encoding (associative), or possibly a combination of the two. Earlier research has indeed found effects of alcohol on associative learning (Parker et al., 1976), but the findings on picture memory are mixed (Yuille and Tollestrup, 1990; Soderlund et al., 2005). It is likely that the associative component makes the task harder, which per se makes it vulnerable to alcohol. The common pattern in the two impaired tasks was that the alcohol group lacked right prefrontal activation, although in slightly different areas, which may correspond to impaired associative encoding of the materials. Also, the logic of the present study was to, in the majority of the tasks, assess the neural processes of encoding by contrasting semantic, associative processing in the experimental condition to perceptual, non-associative processing in the control condition. Recall was only assessed for the semanti-

cally, but not perceptually, processed materials. It is quite likely that incidental encoding occurred in the perceptual condition, but since we did not assess this we cannot make any conclusions about superior encoding in the semantic condition over the perceptual.

In summary, alcohol impaired episodic memory for some materials but not others. When alcohol impaired memory it did so by interfering with activity of regions involved in encoding, such as prefrontal cortex and parahippocampal areas. In addition to our expectations of reduced activation in these areas, some activations became less specific and were present regardless of cognitive process. Hence, as is often the case with the effects of drugs on the brain, the effects of alcohol are complex and influence multiple processes (i.e., both increases and decreases in brain activity). The results from this study are informative about alcohol's effects on the brain, as well as the functional neuroanatomy of human memory.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2006.12.024.

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