ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 31 (2006) 1209 – 1221

Alcohol-induced suppression of BOLD activity during goal-directed visuomotor performance

John Darrell Van Horn,* Melana Yanos, Paul J. Schmitt, and Scott T. Grafton

Department of Psychological and Brain Sciences, Dartmouth College, 6162 Moore Hall, Hanover, NH 03755, USA

Received 12 October 2005; revised 16 January 2006; accepted 20 January 2006
Available online 9 March 2006

The neurophysiological influence of alcohol produces deficits of many cognitive functions, including executive and motor control processes. This study examined the acute effects of alcohol in the context of goal-directed visuomotor performance during functional magnetic resonance imaging (fMRI). Subjects consumed alcohol-laced gelatin during one scan session and non-alcoholic placebo gelatin in another. During each session, subjects performed a visuomotor target capture where they received continuous or terminal positional feedback information. Blood–oxygen level-dependent (BOLD) activity in the cerebellum was suppressed in the presence of alcohol, consistent with the known ethanol sensitivity of the cerebellum. A fronto-parietal network was identified as most affected by alcohol consumption, with differential patterns of BOLD contingent on visual feedback. Results indicate that alcohol selectively suppresses cognitive activity in frontal and posterior parietal brain regions that, in conjunction with cerebellar nuclei, are believed to contribute to the formation of internal cognitive models of motor representation and action.

Introduction

The neurological effects on the motor system characteristic of acute alcohol intoxication in humans are well known—outwardly impaired coordination, resulting in slower, less accurate, and more erratic movements than normal (Solomon and Malloy, 1992). Examinations of the effects of alcohol consumption also implicate a role in higher level cognitive deficits including adverse effects on cognitive control (Curtin and Fairchild, 2003), memory (Kirchner and Sayette, 2003), emotion (Hansenne et al., 2003), response inhibition (Vogel-Sprott et al., 2001), as well as fine motor performance (Zhu et al., 2004). Altered EEG neurophysiological signals in frontal and posterior cortices have been reported following acute alcohol ingestion (Cohen et al., 1993), appearing to alter particular alpha wave signal components (Ehlers et al., 1989), with effects occurring within 35 min after ingestion (Tran et al., 2004). Alcohol-induced reductions in blood oxygenation level-dependent (BOLD)-related signal in primary visual cortex during photic stimulation have also been observed that may have secondary effects on perceptual processes (Calhoun et al., 2004). Automobile driving simulation studies suggest that, in addition to blood alcohol concentration (BAC), measurements of cognitive deficits might be also be used in legally defining intoxication (Brookhuis et al., 2003). However, little is understood about alcohol's influence on the specific cognitive networks involved in the planning, monitoring, updating, integration, and subsequent control of motor output in cognitively demanding, goal-oriented, tasks. These particular systems may be adversely influenced even at concentrations of blood alcohol below the lowest levels considered as legally intoxicated in the U.S. (National Highway Transportation Safety Administration, 2000).

During normal, visually guided, goal-directed movements such as pursuit tracking, a visual representation of a target location must be converted into coordinates appropriate for movement execution (Tong and Flanagan, 2003). Recent studies into the role of movement magnitude (Desmurget et al., 2003), gain (Krakauer et al., 2000), timing (Ivry and Richardson, 2002), and visual feedback (Desmurget et al., 2001) have determined the existence of specific neural subcircuits involved in movement speed, accuracy, and performance tuning. Such studies provide evidence for the notion that the brain constructs and stores internal models of motor control for goal-directed action (Wolpert et al., 1998). Inverse or "forward" models of movement generate sensory or motor consequences for motor actions. These are believed to exist in and be carried out by the cerebellum (Kawato, 1999), which has been supported in part by recent neuroimaging evidence (Miall et al., 2000). These internal representations are essential for predicting the outcomes of movement and making needed online adjustments to maintain movement accuracy (Desmurget and Grafton, 2000).

Visual feedback and its absence, in particular, play central roles in movement monitoring and error detection (Desmurget et al., 2001). Initial learning and the subsequent tuning of forward models require the moment-to-moment assessment and integration of

* Corresponding author. Fax: +1 603 646 1181.
E-mail addresses: John.D.Van.Horn@dartmouth.edu (J.D. Van Horn), Melana.E.S.Yanos.04@Alum.Dartmouth.ORG (M. Yanos), Paul.J.Schmitt.03@Alum.dartmouth.ORG (P.J. Schmitt), Scott.T.Grafton@dartmouth.edu (S.T. Grafton).
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2006.01.020

proprioceptive components and visual inputs describing performance error (Clower and Boussaoud, 2000). The current state of the system is compared against the desired "goal" and a suitable corrective update to the movement computed, requiring the coordination of a distributed network of activity involving cerebellum, basal ganglia, parietal, as well as frontal cortices. Limited visual feedback, e.g., only at the terminal end of movement trajectory, reduces overall performance speed and delays required corrective actions.

Among its range of cognitive effects, alcohol may inhibit activity in the brain areas most needed for such critical motor transformations to occur. A disruption in the network of cortical and cerebellar areas responsible for the efficient execution of movement programs, putatively contributing to the generally poor reaction times observed in studies of motor response, has been observed in alcohol-dependent subjects (Parks et al., 2003), compatible with motor inefficiency and compensatory alterations of cortical–cerebellar circuitry. This would predict altered physiological response in cerebellar, as well as cortical, regions when subjects have alcohol onboard. However, alcohol-dependent effects in cortical areas would be expected in the context of how visuomotor feedback is processed and integrated into internal models—in particular, when visual information about task performance is restricted or absent. The interaction of cortical and cerebellar systems is critical for successful motor performance monitoring and the integration of information during learning. An altered ability to utilize feedback based on task performance at the cortical level could, along with cerebellar deficits, contribute to the poorer motor performance observed in intoxicated individuals and lead to longer term effects in chronic alcohol use. Apart from its overall depression of CNS activity, alcohol may specifically interfere with motor-cognitive processes responsible for the proper integration of visual feedback, proprioceptive, and top-down cognitive mechanisms needed to inform and guide subsequent movement (Ingram et al., 2000).

To investigate the role of acute alcohol consumption on visuomotor function, we used functional magnetic resonance imaging (fMRI) in two separate scanning sessions to examine BOLD signal changes as a function of continuous or terminal visual feedback during the presence or absence of alcohol levels in the body. We expected that alterations in the degree of visual feedback would alter the pattern of BOLD activity; that subjects would show reduced activity in the presence of alcohol compared to placebo; and that there would be significant interaction effects of feedback-by-treatment in areas of the brain known for their contribution to internal models of motor control.

Methods

Subjects

Study participants were $N = 8$ (4 male, 4 female) healthy, right-handed individuals from the Dartmouth College undergraduate and graduate student community, between 21 and 25 years of age (males: 22.75 ± 0.5 years; females: 22.75 ± 2.2 years), and with weights limited to being between 120 to 180 lbs. (males: 150.75 ± 26.96; females: 156.75 ± 17.69). The mean ± SD years of education of the sample was 16.75 ± 1.49 years across both groups. Subjects were chosen from a pool of volunteers who were screened via questionnaire for abnormal alcohol intake and/or history of alcohol abuse or addiction. Volunteers having extremely high or extremely low alcohol tolerances were excluded from participating as potentially confounding study results. Subject handedness was measured and confirmed to be strongly right handed in all subjects according to the Edinburgh Handedness Inventory (Oldfield, 1971). No extraordinary level of motor skill was required to participate in the experiment other than being comfortable using the dial stimulus input device (see below). The study was approved by the Dartmouth Committee for the Protection of Human Subjects (Protocol #16311). Potential subjects received substantial information regarding the purpose of this study and its procedures prior to being admitted. The applicants who were admitted as subjects were briefed on the purpose of the investigation, asked to provide informed consent, and have their weights taken prior to their scheduled participation. Subjects were also asked to refrain from eating for 4 h before their scheduled participation. Female subjects were tested for pregnancy immediately prior to each scanning session. Once the test was confirmed negative for pregnancy, female subjects were allowed to continue their participation.

fMRI study experimental design

Each subject performed a target capture task while lying in the scanner during functional imaging data collection. The subjects controlled a cursor using a quadrature-encoded, fiber optic, fMRI-compatible dial (Fig. 1A) while laying in the MRI scanner bore. The dial received 5V@1A power via a shielded coaxial cable producing no adverse effects on MR image quality. A single 2.54 cm Mylar quadrature-encoded fiber optic encoder (US Digital Corp.) was used to measure dial position, and this information was transmitted using LED transducers (Agilent Technologies) via fiber optic cable to a receiver box located in the scanner control room. Light impulses were converted to digital signals using a National Instruments DAQPad 6070E multi-purpose data acquisition system and these signals used to map cursor position on a dedicated stimulus presentation/response-recording PC. The dial was positioned on a board secured to the thighs of the subject where subjects grasped the dial using their right (dominant) hand. The visuomotor task consisted of fifteen possible circular targets spread evenly along an arc of 108° (Fig. 1B), displayed to the subject in the scanner bore using a back-projection system (Epson Powerlite 7000). For each event of the task, an outline of a circle would appear on the screen, and the subject would place a cursor within the circle by rotating the screwdriver-like input dial device. When subjects "captured" the target circle, i.e., placed the cursor within the circle's boundaries, the area within the circle would immediately illuminate red. After the cursor remained in the circle for 5 s, another target circle would appear in a different location on the screen, and the subject would rotate the dial in the direction of the target once again, capture it, and so forth. A square green box would appear in the position of the center target in between task trials. The subject would place the cursor within the box for a 30-s rest period, after which the next set of target capture trials would begin (Fig. 2).

Performance of the task consisted of rotating the cursor between the pairs of 15-possible targets as quickly but as accurately as possible. Five periods of target capture were separated by 30 s of rest. Two task conditions were presented to each subject on separate task trials: a "concurrent-feedback" condition (CF), in which the cursor is visible on the screen throughout the duration of

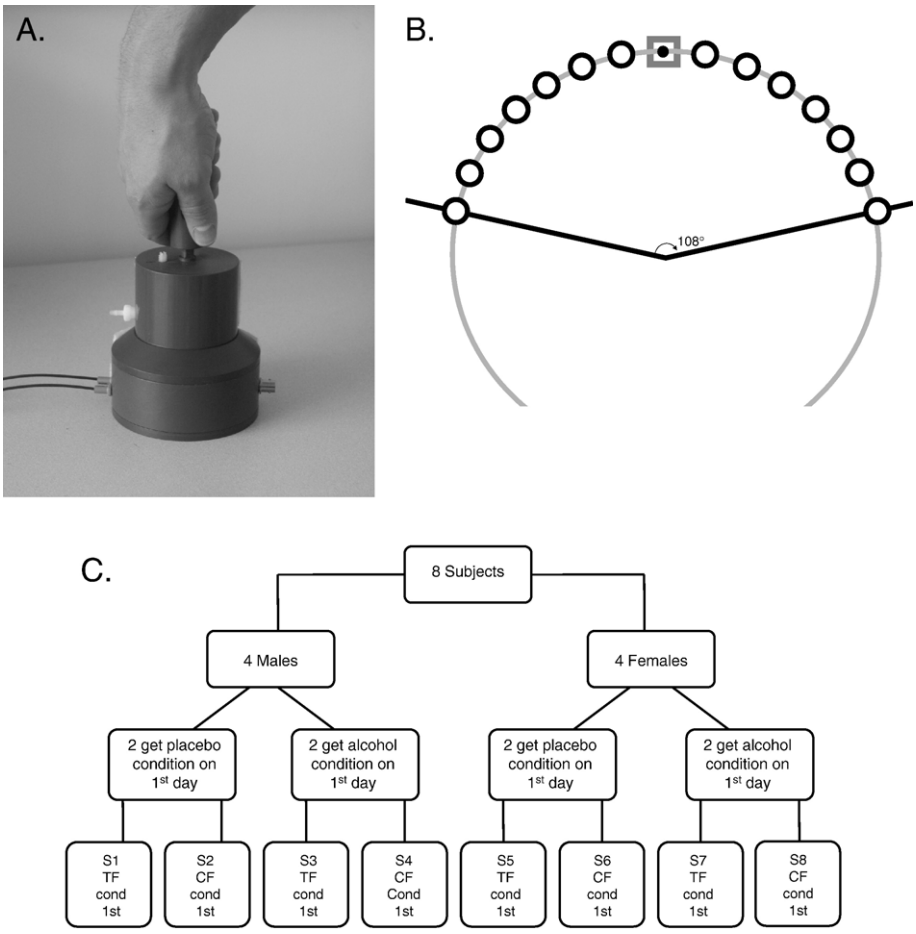

Fig. 1. (A) Dial input device: an MR-compatible dial device was specially constructed using all-plastic materials and utilizing a small fiber-optic transmitter payload. (B) Task paradigm: two versions of this task comprised two levels of secondary variable of this study: (1) the visual feedback (CF) condition, in which the subject performed the task with the aid of a visible cursor; and (2) the without-visual feedback (TF) condition, in which the subject performed the task while the cursor remained hidden. Half of the subjects consisting of two females and two males were randomly selected from their respective gender subgroups and underwent the ALCOHOL condition during the first scanning session and the PLACEBO condition during the second. The remaining two males and two females underwent the PLACEBO condition first, and the ALCOHOL condition second. Those subgroups were then divided again such that half performed the CF version of the task first and the TF condition last during the first scanning session and the vice versa for the second scanning session; conversely, the other half performed the TF condition first and the CF condition last during the first scanning session and the opposite order for the second scanning session. The gray arc is not visible to the subjects but here represents the rotational path of the cursor they control. (C) Subjects and study design: a schematic showing the counter-balanced experimental design of feedback condition and dose of alcohol by scan session.

the task, and a "terminal-feedback" condition (TF) in which it is not visible (see Redding and Wallace, 1988, for discussion). During both conditions, blank targets illuminated in red when the subject-controlled cursor was moved within its boundary. During the CF condition, subjects could use the visual information provided by seeing the cursor to better control movement and subsequent target capture. The absence of cursor information during the TF condition necessitated target capture only on the basis of target illumination. Subjects did not receive any practice on the task prior to entering the scanning environment. Once in the scanner, however, and prior to the beginning of data collection, subjects were allowed <1 min of practice to (re)familiarize themselves with the use of the fiber optic dial device, to view the type of feedback they should expect with and without the visual presence of the cursor.

The experiment was structured as a double-blind matched pairs design (Fig. 1C). There were two levels of the primary independent variable, i.e., alcohol consumption: (1) the subject has consumed a placebo that does not contain any alcohol (PLACEBO condition), and (2) the subject has consumed some alcohol (ALCOHOL condition). A subject's participation consisted of 2 separate days of scanning within 48 h of each other; subjects underwent the ALCOHOL condition on 1 of these 2 days, and the placebo condition on the other. They were informed, however, that they would experience *either* condition for their first and second scan sessions, so that they were unable to predict which treatment they would consume upon their second visit to the study site. Under the ALCOHOL condition, participants consumed a predetermined amount of alcohol which, according to calculations based on Widmarck's equation, would result in a 0.07% BAC level—a level just below the most common BAC limit used in the U.S. for defining legal alcohol intoxication and driving impairment. During the alcohol condition, the necessary fluid ounces of alcohol were determined using Widmark's formula: fl.oz. EtOH = [[BAC g%/ml + (hours since last drink) × Widmark b] × Weight in lbs. × Widmark r]/[0.0514 lb/fl.oz. EtOH × 100% × 1.055 g%/h]. The

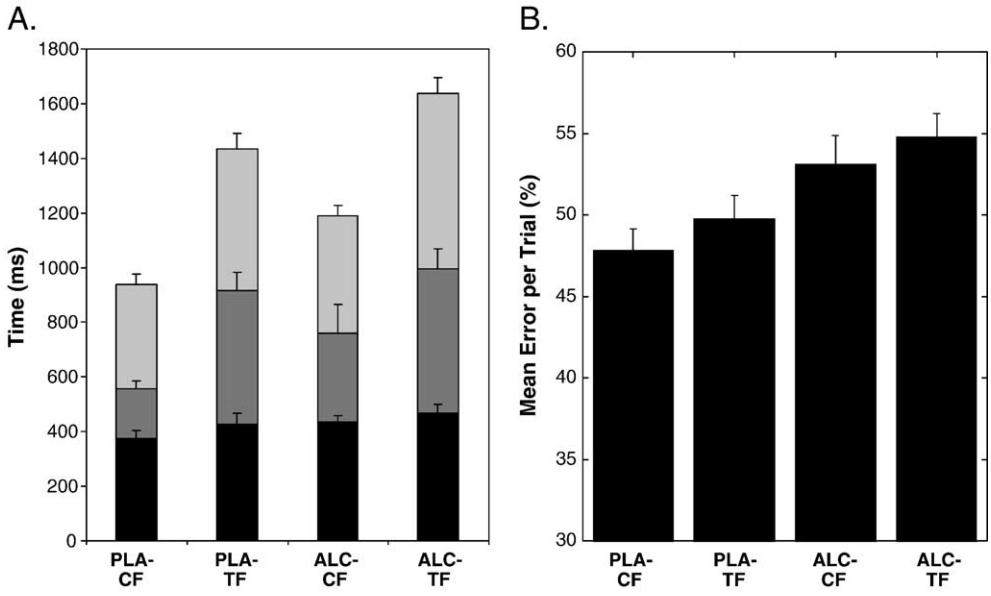

Fig. 2. (A) Subject target capture was divided into submovements (reaction time [black bars], defined as the time between the appearance of a target and the start of the cursor movement; cursor transport [dark gray bars], defined as the time between the start of movement and initial target intercept; and error duration, defined as the time between initial target intercept and the final acquisition of the target). These times were averaged across all movements and each submovement component analyzed using separate repeated measured ANOVAs. Plotted are group means and standard errors for each submovement component. (B) Error was also considered in terms of movement magnitude during the period after initial target intercept. The deviation of the cursor position from target location was computed, taken as an absolute value, summed, and averaged across targets. Values were standardized as a ration to inter-target distance to reflect the magnitude of error as a percentage. Plotted here are mean error percentages across trials and their standard errors.

Widmark b factor was set to 0.017, while the Widmark r factor was set to 0.68 for male and 0.55 female subjects, respectively. Alcohol was administered blindly by having the subjects consume "Jell-O Shots" wherein the typical amount of water per serving was partially replaced with alcohol (100 proof Absolut™ Vodka) and was chilled for at least 4 h at 1°C until set. Four drops of non-alcoholic rum flavoring were added to provide an "alcohol-like" aroma and taste to the mixture.[1]

For the PLACEBO condition, the same amount of gelatin was prepared using water and four drops of the non-alcoholic rum flavoring. A designated investigator (JVH) randomized the substances so that the co-investigator (MY) administering the gelatin would not be aware of which treatment the subject was receiving. A physician (STG) was responsible for overall subject wellness and safety during the experiment. Subjects consumed the gelatin in a room adjacent to the scanner area, and blood alcohol levels were measured with a breathalyzer prior to (as a baseline) and following consumption (to confirm the presence of alcohol in the blood stream). When subjects were placed in the scanner bore, the researchers set up pulmonary and cardiovascular measurement devices to monitor heart rate and respiration throughout the scanning period. These physiological data were observed and recorded by hand every 5 min. Behavioral data of the subject's performance on the target capture task program were recorded onto the computer from which the task program was run and later statistically analyzed. Irrespective of alcohol treatment condition, subjects were escorted to a waiting area following each scan session where they were tested every 15 min using a breathalyzer. Subjects remained in the waiting area for a minimum of 1 h until their blood alcohol level registered at 0% BAC before being allowed to leave the scanning facility. During that time, subjects were also interviewed briefly about their participation in the experiment.

Target capture performance data collection and processing

The position of the cursor was continuously recorded through out each functional imaging run at a rate of ~600 samples/s, the signal decomposed, and analyzed as separate components of movement by computing the temporally weighted moments of their movement trajectories within specifically defined time windows. These components were measured as (i) mean reaction time, defined as the period of time from when a target appeared to when the subject first began their movement to the target; (ii) mean time to peak velocity, measured as the time from initial movement till maximum movement velocity; (iii) the cursor transport phase of movement, defined as the time between the start of movement and the initial target intercept; (iv) mean error duration, the time after initial target capture until the start of the next trial; and (v) mean error magnitude, the amount of positional movement variance following initial target intercept until the start of the next trial. The times obtained (in ms) were averaged across target capture periods from each trial during scanning. Each measure was calculated individually for each subject and analyzed collectively using repeated measures analysis of variance (ANOVA) to examine the main effect of treatment, the main effect visual feedback, as well as the treatment-by-feedback interaction. The data concerning target capture error were additionally examined as the mean positional error taken as a ratio to target width in order to standardize error onto a more meaningful scale. The five movement epochs during which subjects were performing the task versus the 30-s periods of rest were used in subsequent analysis of the fMRI time series data.

[1] Vodka does not have an appreciable "flavor" of its own.

Neuroimage data collection

Neuroimaging data were obtained using a General Electric 1.5 T Signa (Milwaukee, WI, USA) whole body scanner having a gradient strength of 60 mT/m and a slew rate of 40 mT/m/s. Following the collection of a localizer, T1-coplanar, and Spoiled Gradient (SPGR) anatomical images, two T2-weighted echo planar (EPI) functional time series were collected, during which subject performed both versions of the visuomotor task (the CF and TF conditions). EPI data collection parameters were as follows: TR = 2000 ms, TE = 50 ms, FOV = 24 cm, matrix size = 64 × 64, number of slices = 26, slice thickness = 4.5 mm (skip 1 mm), with a total scan duration of 11:40 min. SPGR anatomical image volume parameters were number of echoes = 1, TR = 7.7 ms, TE = 3.0 ms, flip angle = 15, BW = 31.25 MHz, FOV = 240 mm, slice thickness = 1.2 mm, matrix size = 256 × 192, NEX = 2, and a scan duration = 10:21 min. Functional image data collection occurred approximately 20 to 30 min into the experiment, at approximately the point when subject BAC was expected to peak. A total of 1400 EPI functional volumes were collected from each subject (350 for each functional time series, two series executed per session, two sessions per subject).

Neuroimage data processing

Statistical Parametric Mapping (SPM99) brain imaging software (Functional Imaging Laboratory, Institute of Neurology, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm/) was used to preprocess the raw image files for analysis, as well as to apply the images to statistical models in order to calculate the differing BOLD effect between conditions. Because each subject's data were collected on 2 separate days, the process of coregistering and obtaining satisfactory fit of the functional data with the anatomical data involved a parallel data processing pipeline of coregistration, outlined below: functional images were processed within each subject based on the day in which they were collected. Therefore, the 700 images collected on a subject's first session of scanning were realigned separately from the 700 images collected on his/her second session. For the initial step of coregistration, each of two mean functional images was coregistered with the T1-weighted coplanar image that had been collected from the same scan session. In the terminology used by SPM, the coplanar was identified as the "target" image, and the mean within-day functional was identified as the "object" image. All the individual functional imaging volumes for that session were the "other" images included in this round of coregistration. In the second round of coregistration, the coplanar images for each session were coregistered with the mean SPGR anatomical image registered between sessions; the mean SPGR image was selected as target image, and the coplanar image was selected as the object image. The mean functional image and the individual functional imaging volumes were also included in this round of coregistration. The mean anatomical image was first normalized to the mean anatomical SPGR and then normalized to the standardized space of the Montreal Neurological Institute (MNI) brain template. Images were resampled to a voxels size of 2 × 2 × 2 mm. All functional images were spatially smoothed using a 6 × 6 × 6 mm Gaussian kernel. No image volumes were removed from consideration due to excessive subject motion in either the feedback or pharmacological treatment conditions.

Images were analyzed and contrasted according to a block-design model, in which the magnitude of the BOLD effect was measured in terms of when the subject was actively performing the task blocks, minus the BOLD effect for the rest periods. Data were also analyzed as an event-related model, which was used to compare the brain activity between the conditions during the capture of each target, as well as a parametric model, which is used to locate the brain regions that are responsive to the varying rotational distances required during the task that the subject turned the dial in order to capture each target. No appreciable differences were noted in the patterns of results between the separate analytic approaches, so we have chosen here to present only the epoch-related effects. Design matrices had four columns: ALCOHOL/CF, ALCOHOL/TF, PLACEBO/CF, and PLACEBO/TF and were regressed against the preprocessed functional imaging data via the general linear model (GLM). Display of significant patterns of activations as derived from the above statistical contrasts was produced by overlaying group statistical maps on top of standardized neuroanatomy. Results were considered at $P < 0.005$ with a cluster threshold minimum of 10 voxels. Surface renderings of resultant statistically significant BOLD fMRI activity maps were created using the Caret brain surface modeling and display programs from Washington University in St. Louis, MO (http://brainmap.wustl.edu/resources/caretnew.html).

Results

Subject task performance and physiology

Subjects took significantly longer to complete each target capture when under the influence of alcohol [$F(1,7) = 6.67$, $P < 0.05$]. Subjects also took more total time to complete movements without the aid of the visible cursor than when concurrent visual feedback was present [$F(1,7) = 153.77$, $P < 0.001$]. However, no significant interaction between treatment and feedback conditions was observed. Analysis of subject's reaction times showed only a main effect of feedback [$F(1,7) = 15.6$, $P = 0.006$], where times were slower during the TF condition. This was also true for the movement transport phase [$F(1,7) = 121.5$, $P < 0.001$]. The amount of time between initial target intercept until final target capture was likewise only affected by feedback [$F(1,7) = 109.3$, $P < 0.001$]. In this case, however, if the final error correction time was taken as a proportion of total movement time, the main effect of feedback was not found to be significant [$F(1,7) = 3.5$, $P = 0.104$], though a trend toward significance emerged for a treatment-by-feedback interaction [$F(1,7) = 4.8$, $P = 0.065$], suggesting a slightly greater difference between feedback conditions dependent on the presence of alcohol.

The data concerning target capture error were further scrutinized as the mean positional error taken as a ratio to target width. ANOVA results yielded similar findings to each effect of interest in the analysis of mean completion time. When under the influence of alcohol, subjects performed the task with significantly greater error than when they experienced the PLACEBO condition [$F(1,7) = 5.9$, $P < 0.05$]. Likewise, subjects performed with significantly greater error when performing the TF version of the task than when performing the CF condition [$F(1,7) = 18.2$, $P < 0.005$]. However, there was no significant interaction observed between treatment and the form of visual feedback.

Median measurements of cardiac and pulmonary data were obtained from three measurements made at 5-min intervals throughout each MRI run. The median rather than the mean was used in these particular measurements to protect results from being biased by outlier values due to a sudden deep breath or irregularity in subject heart rate. Subjects had a significantly higher heart rate [paired Student's $t(7) = 3.2$, $P < 0.01$] and respiratory rate [paired $t(7) = 3.5$, $P < 0.01$] while under the alcohol condition than the placebo condition.

Effect of target capture movement versus rest

In the comparison of BOLD signal during target capture versus periods of resting state, the pattern of activity reflected a classic pattern of regions typically involved in tasks of motor performance (Table 1A). Significant activation was present in primary (pre- and postcentral gyri; Brodmann's areas (BA) 4 and 2, and supplemental motor cortices in the left cerebral hemisphere. Additionally, there was increased BOLD response in the right inferior frontal gyrus (BA 9) and left supramarginal gyrus (BA 40), cerebellum and precentral gyrus (Fig. 3A). Cortical activation consisted of bilateral activation of superior temporal gyri (BA 22), left inferior parietal cortex (areas BA 7 and 40), and right precentral gyrus (BA 6), which included the premotor area. Results of the Rest versus Movement contrast exhibited relative activity of the cingulate gyrus, precuneus, middle occipital gyrus, middle frontal gyrus, left cerebellum, and right lingual gyrus. The spatial extent of activity in the left hemisphere was considerably greater than in the right, as would be expected in a task in which right-handed subjects used their dominant hand to perform the task.

Main effect of feedback

The main effect for the type of visual feedback was assessed in the contrast of the CF versus TF conditions, collapsed across conditions of treatment (Fig. 3D). This comparison revealed no significant areas of activation in which BOLD signal was greater during CF as compared to the TF condition. However, several brain areas were significantly greater during TF compared to CF (Table 1B), including left SMA (BA 6), cingulate gyrus (BA 31), lingual gyrus (BA 18), cerebellum, and anterior cingulate (BA 24). Right hemisphere areas included the inferior frontal gyrus (BA 47) and the posterior cingulate gyrus (BA 30). The area of the precuneus and cuneus, in particular, has been noted as important in the recall of visuospatial information (Fletcher et al., 1995) and may be involved here out of the need for subjects to visualize cursor trajectory and subsequent target capture in the absence of visual feedback (Grafton et al., 1992).

Table 1A
Regions of significant activation for the main effect of Movement vs. Rest

Region	Brodmann's area	MNI coordinates			Extent	*t* value
		x	*y*	*z*		
Movement > Rest						
Left hemisphere						
Precentral gyrus	4	−32	−23	63	126	7.10
Superior frontal gyrus	6	−10	−11	69	50	5.23
Precuneus	7	−8	−65	61	16	4.89
Postcentral gyrus	2	−51	−26	50	571	4.74
Middle temporal gyrus	21	−65	−38	−8	31	3.92
Supramarginal gyrus	40	−38	−43	53	28	3.79
Right hemisphere						
Inferior frontal gyrus	9	55	10	28	82	8.13
Cerebellum (Lobule VI)		36	−65	−23	38	6.46
Precentral gyrus	6	32	−9	57	96	5.46
Superior temporal gyrus	22	59	−38	20	39	4.60
Rest > Movement						
Left hemisphere						
Cuneus	18	−10	−96	8	103	5.98
Cerebellum (Lobule V/VI)		−20	−40	−20	72	5.73
		−26	−75	−15	32	4.56
Middle frontal gyrus	10	−4	56	14	33	5.72
Superior frontal gyrus	8	−24	37	44	24	4.37
Occipital cortex	19	−44	−77	28	10	4.16
Right hemisphere						
Medial frontal gyrus	10	2	56	3	70	5.82
Lingual gyrus	18	16	−87	−14	19	5.45
Superior frontal gyrus	8	26	28	49	26	4.36
	10	20	53	25	10	3.87
Posterior cingulate	31	22	−91	3	11	3.34
Middle occipital gyrus	18	0	55	27	12	3.33

Results of SPM statistical comparisons of voxel-wise main effects and interactions of movement, ETOH treatment, and visual feedback. Linear contrasts were specified to examine the main effect of movement (A), the main effect of alcohol (B), the main effect of feedback (C), and the interaction of alcohol by feedback (D). All results are presented at $P < 0.005$ with extent threshold of 10 voxels.

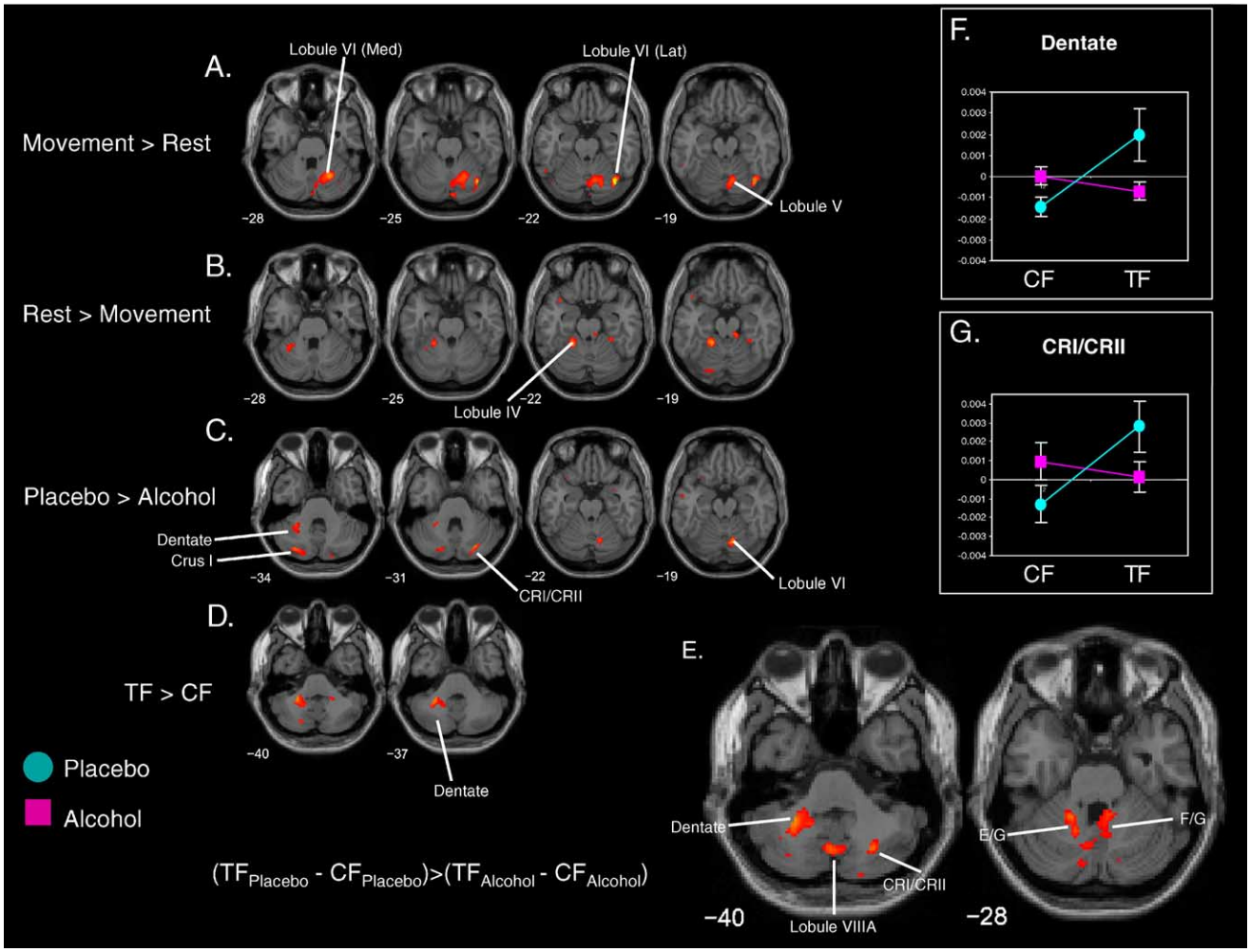

Fig. 3. Group patterns of cerebellar activity were localized against the cerebellar MRI atlas of Schmahmann et al. (2000). Significant ($P < 0.01$) levels of activity were noted in (A) target capture movements versus rest, involving the medial and lateral portions of Lobule VI as well as Lobule V; (B) where resting activity was greater than during movement, largely involving Lobule IV; (C) where placebo was greater than alcohol, largely involving Lobule IV; (D) where the absence of visual feedback showed greater activity than when visual feedback was observed, with relative activity located in the dentate nuclei; and (E) the subregions of the cerebellum showing greater differential activity between feedback conditions (TF-CF) while subjects underwent the placebo condition versus that when they had alcohol on board, indicated significant interaction level BOLD changes in the dentate, Lobule VIIIA, Crus layers I and II, the E/G and F/G deep nuclei. Panels F and G show the standardized beta value of the regression coefficients from the GLM analysis from the peak voxels of the dentate and CRI/CRII cerebellar nuclei. Under placebo, both regions show a significant difference in activity between the CF and TF task conditions (Ps < 0.001). Conversely, when under the influence of alcohol, this difference was not evident (P = ns) nor were the beta coefficients from each condition significantly different from zero. Other cerebellar loci showed identical outcomes. These results suggest that alcohol diminishes the ability of specific cerebellar nuclei to respond to differences in task visual feedback requirements, possibly suppressing the proper utilization of internal models of motor control believed to reside in cerebellar subnuclei.

Main effect of alcohol

Few brain regions showed significantly increased activation during the direct contrast of alcohol versus placebo collapsed across task conditions (Fig. 3B). The bilateral fusiform gyrus (BA 19) in the occipital lobe and the cerebellum in the left hemisphere were identified as showing increased BOLD ac tivation (Table 1C). A greater number of structures were identified as being suppressed by alcohol relative to placebo, including the left inferior and middle frontal gyrus (BAs 47 and 9, respectively), left inferior parietal lobule (BA 40), precuneus, and cerebellum (Figs. 3C and D). In addition, the right middle temporal gyrus (BA 21), left precuneus and cuneus (BAs 31 and 7), right superior and middle frontal gyrus (BA 8), cerebellum, and left inferior parietal lobule (BA 40) all showed greater relative activity during the placebo condition than that of the alcohol condition.

Treatment-by-condition interaction

For the interaction of treatment-by-task-condition [($TF_{Placebo} - CF_{Placebo}$) > ($TF_{Alcohol} - CF_{Alcohol}$)], differential activation was noted in the left superior (BA 10) and right middle frontal gyrus (BA 9) and the cerebellum (Table 1D). Specifically, the cerebellar loci included the dentate, lobule VIIIA, and CRI/CRII nuclei. Most notably differences were observed in bilateral posterior parietal cortex and cuneus (BA 7). These parietal areas and the frontal regions showed the greatest degree of differential BOLD

Table 1B
Regions of significant activation for the main effect of visual feedback

Region	Brodmann's area	MNI coordinates			Extent	*t* value
		x	*y*	*z*		
Continuous feedback > terminal feedback						
<None>						
Terminal feedback > continuous feedback						
Left hemisphere						
Precentral gyrus	6	−50	−2	37	71	7.97
Thalamus (pulvinar)		−12	−35	6	43	6.51
Inferior temporal gyrus	20	−55	−12	−19	24	6.51
Inferior temporal gyrus	20	−51	−52	−11	110	5.87
Inferior frontal gyrus	47	−48	16	−3	92	5.48
Superior temporal gyrus	22	−63	−8	9	28	5.19
Cingulate gyrus	31	−12	−52	29	294	5.10
Lingual gyrus	18	−10	−59	5	43	5.05
Cerebellum (Lobule VI)		−26	−43	−34	67	4.87
Middle temporal gyrus	19	−36	−79	24	24	4.17
Anterior cingulate	24	−2	18	25	34	4.12
Middle frontal gyrus	8	−47	37	40	10	4.12
Right hemisphere						
Inferior frontal gyrus	47	44	16	−6	77	6.29
Posterior cingulate	30	8	−55	10	73	4.21

activity (Fig. 4). No significant effects were present in the reciprocal interaction contrast [e.g., $(TF_{Alcohol} - CF_{Alcohol}) > (TF_{Placebo} - CF_{Placebo})$].

Discussion

The results of this examination indicate that acute consumption of alcohol suppresses the cognitive regions necessary for goal-directed motor action specifically when tasks require the active processing of visual feedback. Evidence involves altered frontal and parietal circuitry as well as a general suppression of cerebellar activity. Moreover, alterations of this system are most dramatically apparent at the neurological level, as evident from fMRI results of a treatment-by-feedback interaction, despite evidence for a lack of a similar interaction in the behavioral results. Suppression in the activity of cerebellar nuclei, such as the dentate, is likely to be critical in this process. Alcohol's negative effects on higher level functioning in the brain indicate a specificity of suppression in areas of motor-related attention and execution, extending to other

Table 1C
Regions of significant activation for the main effect of alcohol

Region	Brodmann's area	MNI coordinates			Extent	*t* value
		x	*y*	*z*		
Alcohol > Placebo						
Left hemisphere						
Cerebellum (Lobule VI)		−34	−83	−15	66	6.04
Fusiform gyrus	19	−44	−74	−12	17	4.76
Right hemisphere						
Fusiform gyrus	19	24	−92	−16	17	5.37
Placebo > Alcohol						
Left hemisphere						
Middle frontal gyrus	46	−42	31	29	232	6.24
Inferior parietal Lobule	40	−44	−56	40	84	5.76
		−60	−37	33	12	4.51
Middle temporal gyrus	39	−32	−71	28	69	5.03
Precuneus	7	−2	−46	62	74	4.90
Inferior frontal gyrus	47	−26	30	−10	50	4.36
Cerebellum (CR I/II)		−26	−74	−33	11	3.68
Right hemisphere						
Precuneus	31	14	−61	21	273	7.76
uperior frontal gyrus	8	18	37	42	56	4.91
Inferior parietal Lobule	40	42	−49	40	32	4.67
Cerebellum (Lobule V/VI)		12	−63	−20	20	4.56
Middle frontal gyrus	8	26	33	42	56	3.92

Table 1D
Regions of significant activation for the alcohol treatment-by-feedback condition interaction

Region	Brodmann's area	MNI coordinates			Extent	*t* value
		x	*y*	*z*		
$(TF_{Placebo} - CF_{Placebo}) > (TF_{Alcohol} - CF_{Alcohol})$						
Left hemisphere						
Superior frontal gyrus	10	−20	57	−6	548	8.70
Cerebellum (Lobule III/IV)		−16	−41	−27	149	6.49
Anterior cingulate	32	−10	22	25	160	5.56
Precuneus	7	−18	−68	32	111	5.50
Anterior cingulate	24	−12	33	4	50	3.45
Right hemisphere						
Middle frontal gyrus	10	32	42	19	288	7.02
Precuneus	19	18	−70	39	340	6.37
Precentral gyrus	6	46	2	36	110	5.85
Medial occipital gyrus	19	34	−75	−7	60	4.72

aspects of functioning besides visuomotor control. The interactions of parietal with frontal brain regions associated with working memory, motor preparation, and action monitoring (D'Esposito et al., 2000) are likely to be of special importance for accurate corrective movements in the absence of a visible target. Though such analyses are not included in this report, additional examination of the fMRI time courses using effective connectivity or dynamic causal modeling would shed additional light on the

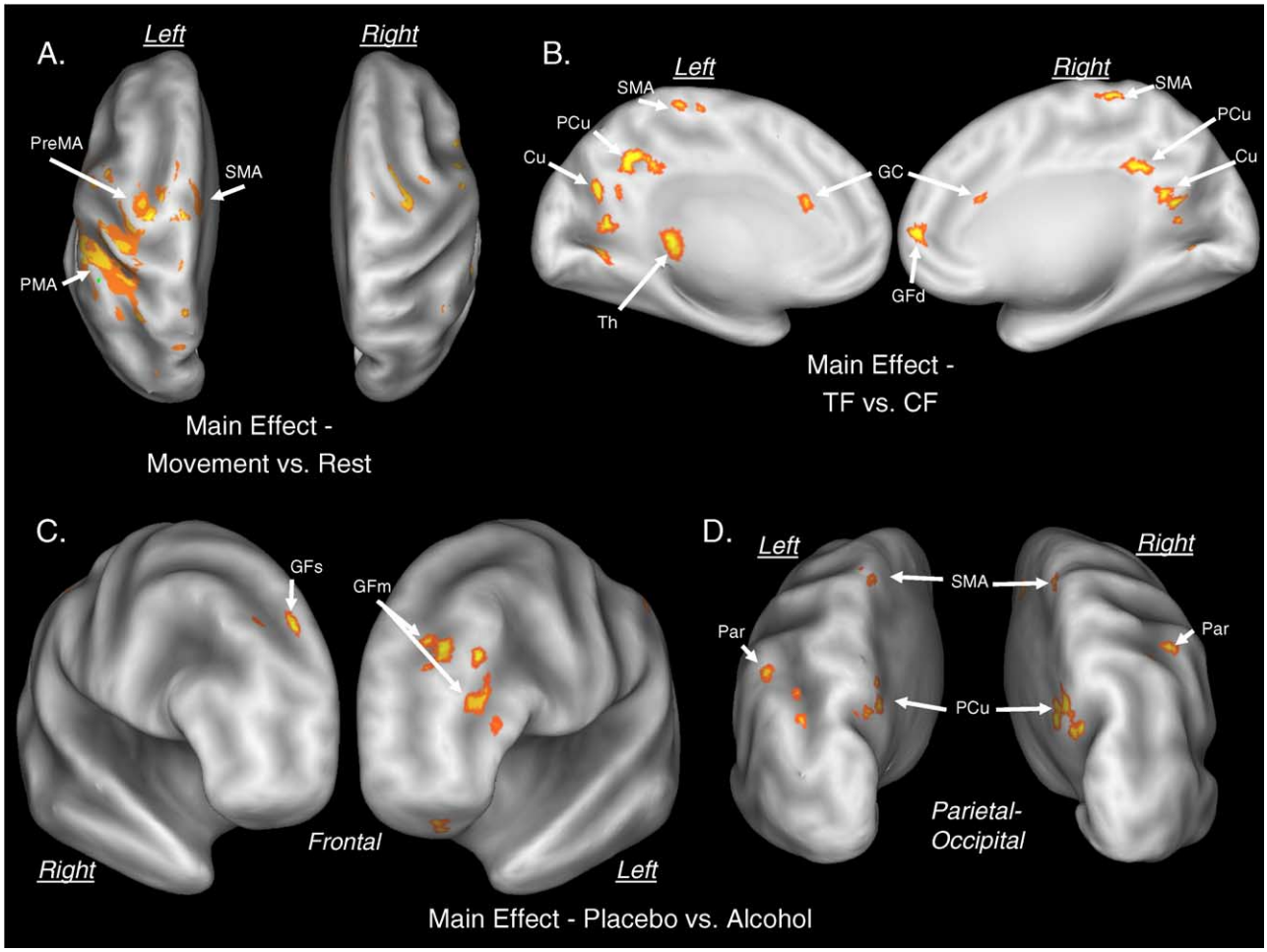

Fig. 4. (A) The main effect of movement versus rest. PreMA = premotor area; SMA = supplemental motor area; PMA = primary motor area. (B) The contrast of no visual feedback versus feedback. Cu = cuneus; PCu = precuneus; GC = cingulate gyrus; GFd = medial frontal gyrus. The reverse contrast showed no significant changes in BOLD activation. (C) The contrast of BOLD EPI signal when subjects were under the influence of alcohol greater than when they were on placebo. GFs = superior frontal gyrus; GFm = middle frontal gyrus. (D) The reverse contrast as in panel C in which brain regions showed BOLD activity greater during placebo than on alcohol. Par = inferior parietal lobule.

complex relationships between these regions. The modeling of inter-regional connectivity will be the topic of future articles using this fMRI task and pharmacological paradigm.

In general, a classic pattern of motor-related activity was observed in subjects during visuomotor target capture compared to a resting state condition. Regions of significant BOLD activity included the pre-, primary, and supplemental motor cortices, as well as the ipsilateral cerebellum. Altering the means of visual feedback, in which subjects could (CT) or could not (TF) view the cursor they manipulated in order to capture each target, showed greater activation in the TF condition versus the CF condition most notably in the left precentral gyrus, left inferior frontal gyrus, left superior temporal gyrus, bilateral cuneus, and cerebellum. Similar patterns of activity have been observed in tasks of shifts of spatial attention (Yantis et al., 2002) or that require the accurate mapping of spatial location (Rao et al., 2003). Given the role of cerebellar nuclei function to movement speed (Turner et al., 2003), precision grip (Monzee et al., 2004), and the constraint of movement (Goodkin and Thach, 2003), these observations agree with the notion that internal models of motor control require cerebellar involvement. Therefore, this provides evidence that these regions contribute to the implementation of internal models of motor action.

The administration of alcohol compared to placebo, collapsed across task conditions, resulted in significant decreases in regions of the primary visual cortex (e.g., area V2) and posterior cingulate with relative increases in fusiform gyrus (BA 19). These results concur with previous reports indicating alcohol's effect on BOLD activity in visual regions, specifically that alcohol-induced alteration of BOLD activity in these areas affects visual perceptual processes. However, alcohol is also known to cause vasodilation (Tawakol et al., 2004) and could affect the hemodynamics of the brain resulting in globally altered T2* signal, regardless of neural activity. Furthermore, heart and respiratory rates in subjects were significantly increased during the alcohol condition. In this case, however, such effects might have manifested themselves as relative global decreases in MR signal across the brain, rather than specific regional decreases in BOLD in areas associated with known involvement in visuomotor performance. Thus, with support from previous studies of alcohol on cognitive processes, we attribute these effects to the experimental manipulation of alcohol within the present cognitive paradigm (also, see below).

Activity in the cerebellum was found to be generally diminished in the presence of alcohol (Fig. 5), in agreement with previous studies indicating cerebellar dysfunction in acute as well as chronic alcohol consumption. The cerebellum is instrumental in movement timing (Ivry, 1997), the processing of fast reaching movements (Spoelstra et al., 2000), and plays a central role in the shaping of motor programs presumably including wide spread cortical involvement. We also observed differential activity in the region of the cerebellar dentate during the TF > CF contrast as well as the interaction of these differences with treatment. Recent findings (Dum and Strick, 2003) have implicated cerebellar projections to the primary motor and premotor regions of the cerebral cortex originate in dorsal portions of the cerebellar dentate, whereas projections to prefrontal and parietal areas originate in more ventral portions of the dentate. Other cerebellar subregions showing significant change as a function of the interaction of condition and treatment included lobules III, IV, V, and VI as well as Crus I. Suppression of activity in dorsal portion of the dentate structure may reduce the ability of subjects to time and carry out rapid movements involved in target capture requiring a shift toward greater cortical involvement. A disruption of fronto-cerebellar circuits may underlie alcohol-related neuropsychological deficits, either by abnormalities present in individual cerebellar subnuclei or by disconnection via interruption of selective circuitry. Extended over years of alcohol usage, the consequences of such suppression may be responsible the frontocerebellar disruption reported in chronic alcoholic patients (Sullivan et al., 2003). Recent evidence also suggests that the genetic sensitivity to the motor-impairing effect of moderate ethanol treatments has a likely biological basis in a single-nucleotide mutation in a cerebellum-specific $GABA_A$ receptor subunit (Korpi, 1994). Studies of patients with progressive cerebellar deficits associated with alcoholism have identified altered cerebellar function as an explanation for the staggering gait typical of intoxicated individuals (Andersen, 2004). However, it is unclear from the present experiment if these cerebellar changes are a functional source of differential activity in cortical areas (e.g., reduced neuronal output meaning reduced activity in cortical areas), or if communication between these regions is part of a broader motor-cognitive system affected by the presence of alcohol. This will be explored in subsequent analyses of these and other data collected using this fMRI task paradigm.

Frontal and parietal areas were also affected by alcohol, indicative of a failure of proper maintenance of internal models. In particular, when the task required greater dependence on internal representation for target capture, i.e., when concurrent visual feedback about position had been removed, alcohol strongly suppressed the pattern of fronto-parietal region activity (Fig. 4)—a collection of brain areas previously implicated as being necessary for the formation and updating of internal models of visuomotor control (Grafton et al., 1998). This suggests that the neural computations for movement to a visual goal, as well as the eliciting of a preplanned motor response as an expression of movement intention, are being particularly affected in the presence of alcohol. Conversely, the general suppression in cerebellar nuclei activity under the alcohol versus placebo contrast may reflect the failure of an essential motor mechanism dependent upon the form of visual feedback.

The involvement of frontal regions agrees with recent observations that the PFC is involved in action preparation (Pochon et al., 2001). The PFC may also serve as the central node in the allocation of resources to the processing of novel events and error monitoring, whereas the posterior parietal lobe may provide the neural substrate for the dynamic process of updating the internal model of the environment to account for such events (Daffner et al., 2003). Parietal/Premotor networks have been argued as only minimally sufficient to store visuospatial information in short-term memory; thus, the PFC may also be needed in the preparation of action stored in memory. In the task used in this study, components of movement preparation are required given the need to match direction of dial rotation needed for target capture, etc. In addition, the frontal–parietal system has been noted to be particularly sensitive to components of stimulus event novelty (Barcelo et al., 2002) possibly engaging here in reaction to the apparent novelty of new target locations being presented. Alcohol-dependent effects in these areas have been previously reported and possibly contribute to general slowing of average movement completion times observed in our subjects. Alteration

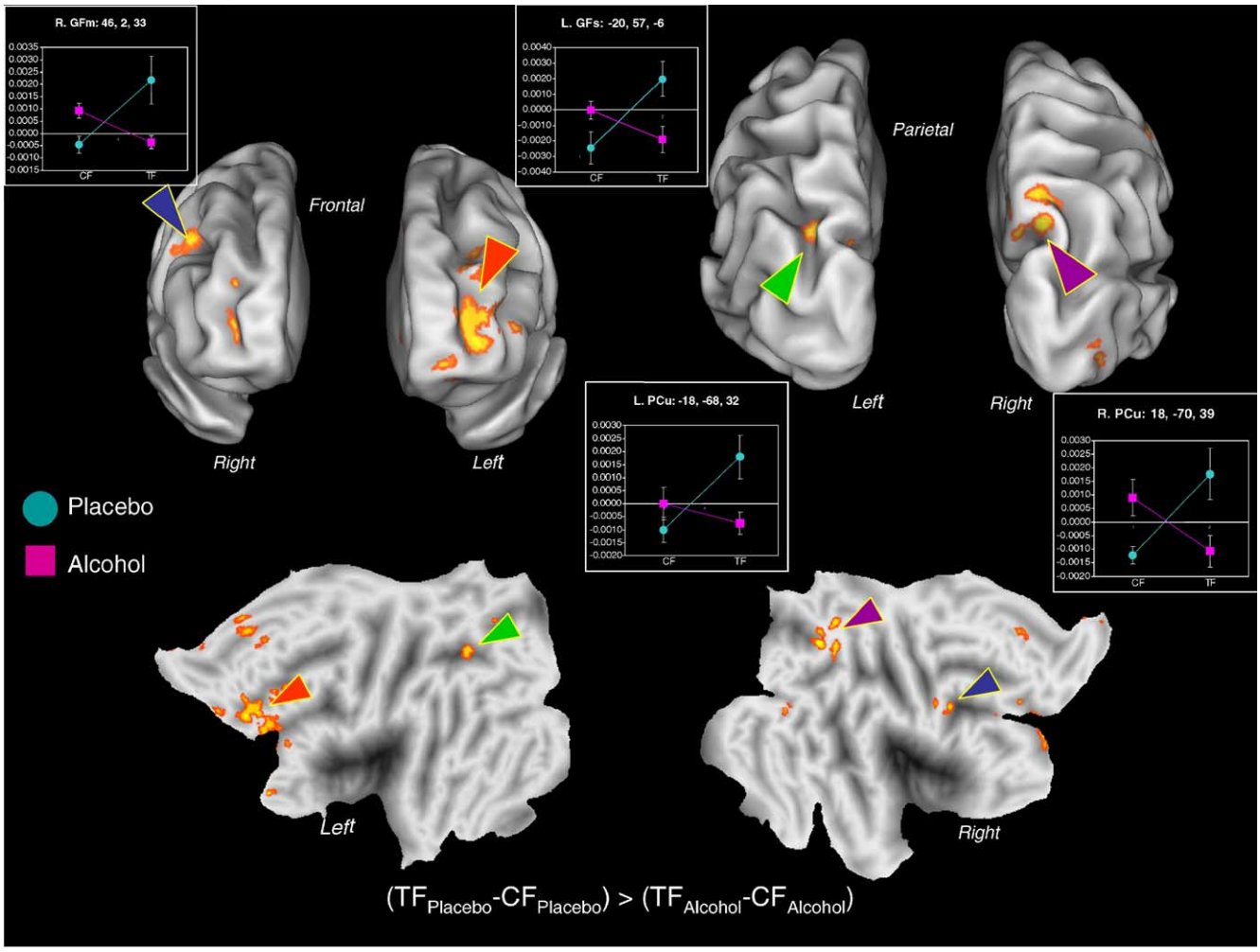

Fig. 5. Cortical surface model rendering of the interaction of feedback-by-treatment in BOLD signal. Statistically larger differential activity between having no visual feedback and its presence while subjects were on placebo versus the alcohol treatment was noted in bilateral posterior parietal cortex (BA 7) as well as in left middle (BA 9/10) and right superior frontal gyri.

of activity in these areas with alcohol may reflect a reduced ability of internal models to properly integrate stimulus and performance feedback information.

In non-human primates, posterior parietal neurons have been found to encode signals related to the perception of space (Bremmer et al., 2001), time (Leon and Shadlen, 2003), and is important in comparing current motor output with motor expectations (Gardner et al., 2002). In humans, posterior parietal areas have been found to be important in the control of smooth pursuit eye movements—notably target position prediction, visuo-spatial attention and transformation, multimodal visuomotor control. However, it is the role of the parietal cortex in the forward modeling of movement, serving as a comparator of the current movement against that needed for goal completion, which may be being affected by the presence of alcohol. Failure to properly generate movement error-related corrections in the forward model feed-back loop would slow movement timing and increase target capture errors. The results of this study support the notion that human PPC may be more involved in goal-oriented limb movements, analogous to its role in the primate (Simon et al., 2002), consistent with other evidence from human imaging studies, but that this role is compromised by alcohol. That is, alcohol may disrupt the ability of these brain regions to properly compute corrective movements needed to update internal models and anticipate motor output requirements.

In general, subjects performed more slowly and with less accuracy under the alcohol condition. The absence of visual feedback resulted in slower overall completion as well as increases in positional error. However, we noted no statistically significant behavioral treatment-by-task-condition interaction of task completion time or performance error. Thus, alcohol's effects were observed to be generally suppressive and not conditional on feedback at the behavioral level, despite there being a strong interaction evident in the BOLD fMRI data. These somewhat counter-intuitive effects are similar to previous neuroimaging pharmacological studies using gonadal steroid (Berman et al., 1997) and amphetamine (Mattay et al., 1996) and their effects on rCBF which also did not show behavioral treatment-by-condition interactions despite dramatic pharmacologically related effects in task-dependent rCBF. Previous work has indicated that spatial attentional systems may be particularly sensitive to pharmacological manipulation, e.g., enhanced by methylphenidate and attenuated by sulpiride in response to task load requirements (Bullmore et al., 2003). This may be true in the case of the systems underlying performance in this task. But

while BOLD signal interaction effects may reflect alterations in the neural contributions to task performance, these may compensate and bolster task performance in cases of mild alcohol intoxication. At higher levels of alcohol intoxication, feedback processing compensatory systems may break down at the expense of over all task performance.

We note several caveats which may influence the interpretation of these findings. Firstly, the relatively small number of subjects in the present study may constrain broad population generalizability and statistical power. However, subjects were scanned on two occasions in a completely counter-balanced fashion which is a strength of this particular experimental design. Secondly, we specifically selected subjects with moderate alcohol consumption histories. A more thorough examination of the range of alcohol tolerances would have included subjects at the extremes of consumption and utilized this history as a factor of interest. Thirdly, the sampling of blood alcohol level using the breathalyzer was only possible when subjects were outside of the high-field magnetic environment. This meant that the precise magnitude and point-in-time of peak BAC could not be determined. While continuous blood sampling would have permitted greater precision in both regards, substantial technical limitations meant that this was not possible in the present study. Also, a broad range of possible approaches exist for the analysis of the visuomotor behavioral time course data beyond that we report here. Such approaches should be investigated to determine the most suitable method for characterizing moment-to-moment variation in performance and how it might be affected in the presence of alcohol. Lastly, while cardiac and respiratory measurements were made periodically throughout each fMRI scan session and a significant difference was observed between placebo and alcohol treatments, these data were not such that they could be used to inform the GLM analysis of brain image data. In general, the effects of pharmacological manipulations on the BOLD signal and the role of the physiological responses to such treatments in detecting BOLD change are not entirely understood. However, the examination of power-law effects to pharmacological manipulations (Arthurs et al., 2004) indicate that they influence BOLD signal "gain" but not the slope of exponential increases with stimulus saliency and that physiological changes contribute only slightly to the overall variance explained. Thus, pharmacological manipulations result in observable cognitive change independent of peripheral physiological alterations. Future studies based upon this visuo-motor/alcohol manipulation paradigm will seek to maximize cohort size, broaden its scope, and examine more closely these important physiological variables.

Despite some limitations, the outcomes of the present study provide compelling evidence for the significant impairment of neural systems critical for feedback monitoring and the updating of motor outputs. The amounts of alcohol used in this study reflect amounts typically consumed in social drinking and the performance effects observed would be expected to be more pronounced at higher weight/gender titrated treatments of alcohol. This study demonstrates the utility of using alcohol as a cognitive probe in the visuomotor domain, and that its interaction with visual feedback is an important component in understanding the systems most affected in acute alcohol consumption. Additionally, as a consequence of such suppression in brain systems essential for the maintenance of internal models and, putatively, the skilled operation of motor vehicles, further consideration should, therefore, be given to using BAC limits as the primary definition of alcohol intoxication and the development of tests more sensitive to subtle impairments of internal models and brain systems dependent on feedback processing.

Acknowledgments

This work is supported by the NSF (01-41 BCS-0121905) to JVH, the NINDS (PO1 NS044393) to STG, and Dartmouth College sponsored Richter Grant, Marie A. Center 1982 Memorial Fund, and Susan L. Burkhardt 1982 Award to MY. The authors wish to thank Eugene Tunik and Scott Johnson-Frey for their helpful discussion, Jesse Calhoun for assistance in data collection, Richard Johnson and Fredrick Woods in the construction of the non-ferrous dial device, and Tammy Laroche for MRI technical expertise. The raw and processed echo planar imaging (EPI) time series volumes, all anatomical image volumes, statistical results images, and study meta-data (including scanner protocols, subject demographics, behavioral data, etc.), from this investigation will be made publicly available through the fMRI Data Center (http://www.fmridc.org).

References

Andersen, B.B., 2004. Reduction of Purkinje cell volume in cerebellum of alcoholics. Brain Res. 1007 (1–2), 10–18.

Arthurs, O.J., Stephenson, C.M., Rice, K., Lupson, V.C., Spiegelhalter, D.J., Boniface, S.J., Bullmore, E.T., 2004. Dopaminergic effects on electrophysiological and functional MRI measures of human cortical stimulus–response power laws. NeuroImage 21 (2), 540–546.

Barcelo, F., Perianez, J.A., Knight, R.T., 2002. Think differently: a brain orienting response to task novelty. NeuroReport 13 (5), 1887–1892.

Berman, K.F., Schmidt, P.J., Rubinow, D.R., Danaceau, M.A., Van Horn, J.D., Esposito, G., Ostrem, J.L., Weinberger, D.R., 1997. Modulation of cognition-specific cortical activity by gonadal steroids: a positron-emission tomography study in women. Proc. Natl. Acad. Sci. U. S. A. 94 (16), 8836–8841.

Bremmer, F., Schlack, A., Duhamel, J.R., Graf, W., Fink, G.R., 2001. Space coding in primate posterior parietal cortex. NeuroImage 14 (1 Pt. 2), S46–S51.

Brookhuis, K.A., De Waard, D., Fairclough, S.H., 2003. Criteria for driver impairment. Ergonomics 46 (5), 433–445.

Bullmore, E., Suckling, J., Zelaya, F., Long, C., Honey, G., Reed, L., Routledge, C., Ng, V., Fletcher, P., Brown, J., Williams, S.C., 2003. Practice and difficulty evoke anatomically and pharmacologically dissociable brain activation dynamics. Cereb. Cortex 13 (2), 144–154.

Calhoun, V.D., Altschul, D., McGinty, V., Shih, R., Scott, D., Sears, E., Pearlson, G.D., 2004. Alcohol intoxication effects on visual perception: an fMRI study. Hum. Brain Mapp. 21 (1), 15–26.

Clower, D.M., Boussaoud, D., 2000. Selective use of perceptual recalibration versus visuomotor skill acquisition. J. Neurophysiol. 84 (5), 2703–2708.

Cohen, H.L., Porjesz, B., Begleiter, H., 1993. Ethanol-induced alterations in electroencephalographic activity in adult males. Neuropsychopharmacology 8 (4), 365–370.

Curtin, J.J., Fairchild, B.A., 2003. Alcohol and cognitive control: implications for regulation of behavior during response conflict. J. Abnorm. Psychol. 112 (3), 424–436.

Daffner, K.R., Scinto, L.F., Weitzman, A.M., Faust, R., Rentz, D.M., Budson, A.E., Holcomb, P.J., 2003. Frontal and parietal components of a cerebral network mediating voluntary attention to novel events. J. Cogn. Neurosci. 15 (2), 294–313.

Desmurget, M., Grafton, S., 2000. Forward modeling allows feedback control for fast reaching movements. Trends Cogn. Sci. 4 (11), 423–431.

Desmurget, M., Grea, H., Grethe, J.S., Prablanc, C., Alexander, G.E., Grafton, S.T., 2001. Functional anatomy of nonvisual feedback loops during reaching: a positron emission tomography study. J. Neurosci. 21 (8), 2919–2928.

Desmurget, M., Grafton, S.T., Vindras, P., Grea, H., Turner, R.S., 2003. Basal ganglia network mediates the control of movement amplitude. Exp. Brain Res. 153 (2), 197–209.

D'Esposito, M., Ballard, D., Zarahn, E., Aguirre, G.K., 2000. The role of prefrontal cortex in sensory memory and motor preparation: an event-related fMRI study. NeuroImage 11 (5 Pt. 1), 400–408.

Dum, R.P., Strick, P.L., 2003. An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. J. Neurophysiol. 89 (1), 634–639.

Ehlers, C.L., Wall, T.L., Schuckit, M.A., 1989. EEG spectral characteristics following ethanol administration in young men. Electroencephalogr. Clin. Neurophysiol. 73 (3), 179–187.

Fletcher, P.C., Frith, C.D., Baker, S.C., Shallice, T., Frackowiak, R.S., Dolan, R.J., 1995. The mind's eye—Precuneus activation in memory-related imagery. NeuroImage 2 (3), 195–200.

Gardner, E.P., Debowy, D.J., Ro, J.Y., Ghosh, S., Babu, K.S., 2002. Sensory monitoring of prehension in the parietal lobe: a study using digital video. Behav. Brain Res. 135 (1–2), 213–224.

Goodkin, H.P., Thach, W.T., 2003. Cerebellar control of constrained and unconstrained movements: I. Nuclear inactivation. J. Neurophysiol. 89 (2), 884–895.

Grafton, S.T., Mazziotta, J.C., Woods, R.P., Phelps, M.E., 1992. Human functional anatomy of visually guided finger movements. Brain 115 (Pt. 2), 565–587.

Grafton, S.T., Fagg, A.H., Arbib, M.A., 1998. Dorsal premotor cortex and conditional movement selection: a PET functional mapping study. J. Neurophysiol. 79 (2), 1092–1097.

Hansenne, M., Olin, C., Pinto, E., Pitchot, W., Ansseau, M., 2003. Event-related potentials to emotional and neutral stimuli in alcoholism. Neuropsychobiology 48 (2), 77–81.

Ingram, H.A., van Donkelaar, P., Cole, J., Vercher, J.L., Gauthier, G.M., Miall, R.C., 2000. The role of proprioception and attention in a visuomotor adaptation task. Exp. Brain Res. 132 (1), 114–126.

Ivry, R., 1997. Cerebellar timing systems. Int. Rev. Neurobiol. 41, 555–573.

Ivry, R.B., Richardson, T.C., 2002. Temporal control and coordination: the multiple timer model. Brain Cogn. 48 (1), 117–132.

Kawato, M., 1999. Internal models for motor control and trajectory planning. Curr. Opin. Neurobiol. 9 (6), 718–727.

Kirchner, T.R., Sayette, M.A., 2003. Effects of alcohol on controlled and automatic memory processes. Exp. Clin. Psychopharmacol. 11 (2), 167–175.

Korpi, E.R., 1994. Role of GABAA receptors in the actions of alcohol and in alcoholism: recent advances. Alcohol Alcohol. 29 (2), 115–129.

Krakauer, J.W., Pine, Z.M., Ghilardi, M.F., Ghez, C., 2000. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J. Neurosci. 20 (23), 8916–8924.

Leon, M.I., Shadlen, M.N., 2003. Representation of time by neurons in the posterior parietal cortex of the macaque. Neuron 38 (2), 317–327.

Mattay, V.S., Berman, K.F., Ostrem, J.L., Esposito, G., Van Horn, J.D., Bigelow, L.B., Weinberger, D.R., 1996. Dextroamphetamine enhances "neural network-specific" physiological signals: a positron-emission tomography rCBF study. J. Neurosci. 16 (15), 4816–4822.

Miall, R.C., Imamizu, H., Miyauchi, S., 2000. Activation of the cerebellum in co-ordinated eye and hand tracking movements: an fMRI study. Exp. Brain Res. 135 (1), 22–33.

Monzee, J., Drew, T., Smith, A.M., 2004. Effects of muscimol inactivation of the cerebellar nuclei on precision grip. J. Neurophysiol. 91 (3), 1240–1249.

National Highway Transportation Safety Administration, 2000. Impaired Driving in the United States. Retrieved December 15th, 2004, 2004, from http://www.nhtsa.dot.gov/people/injury/alcohol/impaired-drivingusa/US.pdf.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.

Parks, M.H., Morgan, V.L., Pickens, D.R., Price, R.R., Dietrich, M.S., Nickel, M.K., Martin, P.R., 2003. Brain fMRI activation associated with self-paced finger tapping in chronic alcohol-dependent patients. Alcohol.: Clin. Exp. Res. 27 (4), 704–711.

Pochon, J.B., Levy, R., Poline, J.B., Crozier, S., Lehericy, S., Pillon, B., Deweer, B., Le Bihan, D., Dubois, B., 2001. The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study. Cereb. Cortex 11 (3), 260–266.

Rao, H., Zhou, T., Zhuo, Y., Fan, S., Chen, L., 2003. Spatiotemporal activation of the two visual pathways in form discrimination and spatial location: a brain mapping study. Hum. Brain Mapp. 18 (2), 79–89.

Redding, G.M., Wallace, B., 1988. Adaptive mechanisms in perceptual-motor coordination: components of prism adaptation. J. Mot. Behav. 20 (3), 242–254.

Schmahmann, J.D., Doyon, J., Toga, A.W., Petrides, M., Evans, A., 2000. MRI Atlas of the Human Cerebellum. Academic Press, San Diego.

Simon, S.R., Meunier, M., Piettre, L., Berardi, A.M., Segebarth, C.M., Boussaoud, D., 2002. Spatial attention and memory versus motor preparation: premotor cortex involvement as revealed by fMRI. J. Neurophysiol. 88 (4), 2047–2057.

Solomon, D.A., Malloy, P.F., 1992. Alcohol, head injury, and neuropsychological function. Neuropsychol. Rev. 3 (3), 249–280.

Spoelstra, J., Schweighofer, N., Arbib, M.A., 2000. Cerebellar learning of accurate predictive control for fast-reaching movements. Biol. Cybern. 82 (4), 321–333.

Sullivan, E.V., Harding, A.J., Pentney, R., Dlugos, C., Martin, P.R., Parks, M.H., Desmond, J.E., Chen, S.H., Pryor, M.R., De Rosa, E., Pfefferbaum, A., 2003. Disruption of frontocerebellar circuitry and function in alcoholism. Alcohol.: Clin. Exp. Res. 27 (2), 301–309.

Tawakol, A., Omland, T., Creager, M.A., 2004. Direct effect of ethanol on human vascular function. Am. J. Physiol. Heart. Circ. Physiol. 286 (6), H2468–H2473.

Tong, C., Flanagan, J.R., 2003. Task-specific internal models for kinematic transformations. J. Neurophysiol. 90 (2), 578–585.

Tran, Y., Craig, A., Bartrop, R., Nicholson, G., 2004. Time course and regional distribution of cortical changes during acute alcohol ingestion. Int. J. Neurosci. 114 (7), 863–878.

Turner, R.S., Desmurget, M., Grethe, J., Crutcher, M.D., Grafton, S.T., 2003. Motor subcircuits mediating the control of movement extent and speed. J. Neurophysiol. 90 (6), 3958–3966.

Vogel-Sprott, M., Easdon, C., Fillmore, M., Finn, P., Justus, A., 2001. Alcohol and behavioral control: cognitive and neural mechanisms. Alcohol.: Clin. Exp. Res. 25 (1), 117–121.

Wolpert, D.M., Goodbody, S.J., Husain, M., 1998. Maintaining internal representations: the role of the human superior parietal lobe. Nat. Neurosci. 1 (6), 529–533.

Yantis, S., Schwarzbach, J., Serences, J.T., Carlson, R.L., Steinmetz, M.A., Pekar, J.J., Courtney, S.M., 2002. Transient neural activity in human parietal cortex during spatial attention shifts. Nat. Neurosci. 5 (10), 995–1002.

Zhu, W., Volkow, N.D., Ma, Y., Fowler, J.S., Wang, G.J., 2004. Relationship between ethanol-induced changes in brain regional metabolism and its motor, behavioural and cognitive effects. Alcohol Alcohol. 39 (1), 53–58.