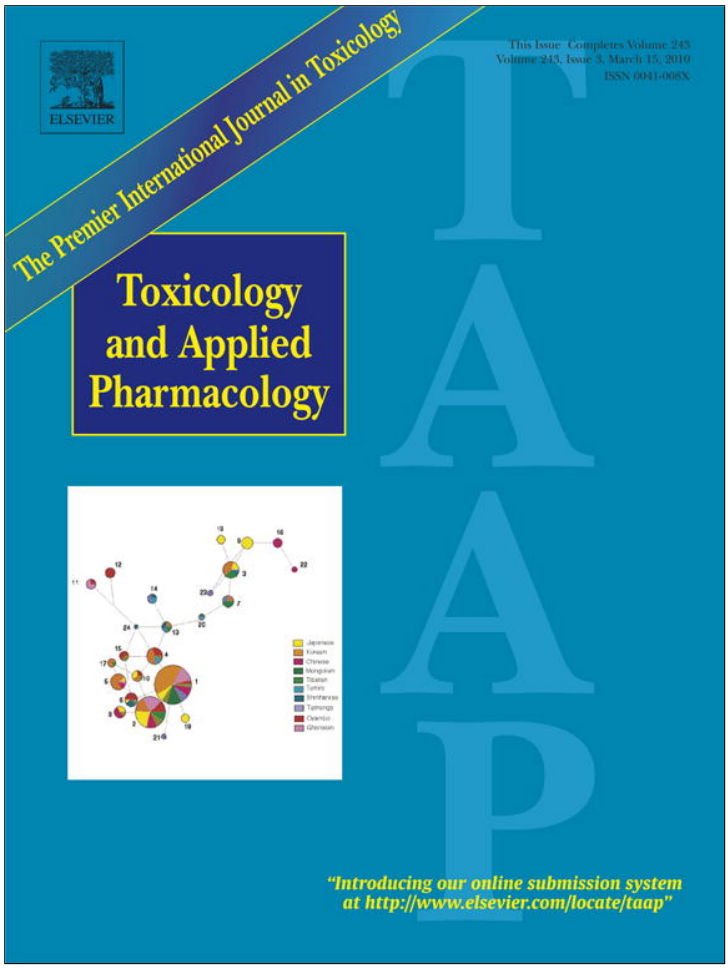

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The effects of acute alcohol exposure on the response properties of neurons in visual cortex area 17 of cats

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ABSTRACT

Physiological and behavioral studies have demonstrated that a number of visual functions such as visual acuity, contrast sensitivity, and motion perception can be impaired by acute alcohol exposure. The orientation- and direction-selective responses of cells in primary visual cortex are thought to participate in the perception of form and motion. To investigate how orientation selectivity and direction selectivity of neurons are influenced by acute alcohol exposure *in vivo*, we used the extracellular single-unit recording technique to examine the response properties of neurons in primary visual cortex (A17) of adult cats. We found that alcohol reduces spontaneous activity, visual evoked unit responses, the signal-to-noise ratio, and orientation selectivity of A17 cells. In addition, small but detectable changes in both the preferred orientation/direction and the bandwidth of the orientation tuning curve of strongly orientation-biased A17 cells were observed after acute alcohol administration. Our findings may provide physiological evidence for some alcohol-related deficits in visual function observed in behavioral studies.

Introduction

Alcohol has widespread systemic effects on the central nervous system, where it influences various aspects of neurotransmitters involved in visual processing. The physiological effects are reflected in a variety of changes in visual perception, including spatial–frequency discrimination (Watten et al., 1998), contrast sensitivity (Nicholson et al., 1995), depth perception (Hill and Toffolon, 1990), visual acuity (Wilson and Mitchell, 1983), and contrast discrimination performance (Pearson and Timney, 1999). However, much of the literature, while providing excellent description of deficits that may occur, has not specifically addressed the physiological mechanisms that might mediate these deficits.

The neurophysiological effects of alcohol can be monitored in terms of changes in neuronal activity in various regions of the brain (Klemm et al., 1976). For instance, an early study has demonstrated a dose-dependent inhibitory effect of alcohol on the spontaneous activity of single cells in the dorsal hippocampus (Grupp, 1980). More recently, it has been demonstrated that alcohol could quickly abolish both auditory and visual responses from hippocampal granule cells (Huang and Huang, 2007). Thus, a potentially fruitful approach to understanding the physiological mechanisms mediating alcohol-related impairments in visual perception is to analyse the ways in which acute alcohol exposure influences the electrical activity of neurons in the visual cortex. In this regard, numerous past studies have examined the influence of acute alcohol on the visual evoked potential (VEP) recorded from both human and other animal subjects (Salamy and Williams, 1973; Neill et al., 1991; Hetzler and Bednarek, 2001) and have provided an integrated view of alcohol-related changes in neural activity and sensory processing. However, these studies did not address the influence of alcohol on the response properties of individual cortical cells, which is necessary for, and imposes constraints on, visual perception.

Orientation selectivity and direction selectivity, which refer to the selective response to both the angular orientation and the direction of motion of lines, bars, and edges (Hubel and Wiesel, 1959), are fundamental properties of most neurons in the primary visual cortex and are thought to participate in the perception of form and motion (Zhan and Shou, 2002; Leventhal et al., 2003). However, although alcohol-related deficits in visual perception and motion discrimination have been widely investigated in behavioral studies (Wilson and Mitchell, 1983; Hill and Toffolon, 1990; Neill et al., 1991; Pearson and Timney, 1999), there have been few studies on the effect of acute alcohol exposure on the orientation and direction preference at the cellular electrophysiological level. It has been suggested that functional changes of cortical neurons, including the decreased orientation and direction selectivity of A17/V1 neurons occurring in old cats and aged monkeys, might underlie various types of visual perception degradation occurring during aging (Schmolesky et al., 2000; Hua et al., 2006). Similarly, the investigation of effects of alcohol on orientation/direction selectivity of cortical cells could be helpful

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for better understanding the mechanism by which alcohol impairs many aspects of visual perception.

We have explored the effect of acute alcohol exposure on the response properties of A17 cells in cats using the extracellular single-unit recording method. In addition, we have investigated the effect of acute alcohol exposure on the tuning curve profiles of strongly orientation-biased cells. We found a dose-dependent effect of alcohol on the orientation selectivity as well as the responsiveness of A17 neurons. We also observed a small shift in preferred orientation and direction of strongly orientation-biased A17 cells after acute alcohol administration. Our findings provide a possible physiological explanation for some of the alcohol-related impairments in visual perception.

Materials and methods

Subjects. Experiments were performed on anesthetized and paralyzed adult cats. All seven cats were confirmed ophthalmoscopically to have no optical or retinal problems before the experiment. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Science and Technology of China and conformed to the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Preparation for extracellular recording. The preparation for extracellular single-unit recording was as described (Hua et al., 2006). Briefly, cats were anesthetized before surgery with ketamine HC1 (20 mg/kg, i.m.; Ben Venue Lab Inc., Bedford, OH, USA) and then the intravenous and tracheal cannulae were inserted. A long-acting anesthetic (1% lidocaine HCl; Abbott Labs, Chicago, IL, USA) was applied to all wound margins and pressure points. Cats were then placed in a stereotaxic apparatus. Neosynephrine (0.5%; Bayer, Morristown, NJ, USA) was administered to retract the nictitating membranes. Pupils were maximally dilated with atropine and appropriate contact lenses were used to protect the corneas.

A mixture of urethane (20 mg/kg/h; SCR, Shanghai, China) and gallamine triethiodide (10 mg/kg/h; Sigma) was infused i.v. to maintain anesthesia and paralysis. Expired pCO_2 was maintained at approximately 4%. Heart rate (about 180–220 pulses/min) and EEG were monitored throughout the experiment to assess the level of anesthesia. A small hole was drilled in the skull 4 mm posterior to the ear bars and 2 mm lateral to the midline. A glass microelectrode filled with 2 M NaCl (with an impedance of 3–5 MΩ) was positioned and advanced using a hydraulic micromanipulator (NARISHIGE, Japan). The small hole was filled with a 4% solution of agar in saline and sealed with wax after introduction of the electrode assembly. At the end of data collection, the animal was killed by an overdose of pentobarbital.

Visual stimulation. Visual stimulus patterns were drifting sinusoidal gratings shown on a CRT monitor (1024×768, 85 Hz, G220; Sony, Japan), placed 57 cm away from the cat's eyes. The program to generate the stimulus was written in MATLAB, using the extensions provided by the high-level Psychophysics Toolbox (Brainard, 1997) and the low-level Video Toolbox (Pelli, 1997). When a single unit was isolated, the cell's receptive field was carefully mapped by consecutively presenting a series of computer-generated light spots on the CRT. Then, a set of sinusoidal gratings with optimal stimulus parameters, moving in 16 different directions (0°–360° scale with an increment of 22.5°) was used to compile the orientation tuning curves. The orientation of each drifting stimulus was orthogonal to its direction of motion. The Michaelson contrast of the stimuli was 99%. The mean luminance of the display was 45.2 cd/m^2, and the environment luminance on the cornea was 0.1 lx.

Data collection and analysis. After the signal was amplified with an extracellular amplifier (DAGAN 2400A, USA), action potentials were fed into a window discriminator with audio monitor. The original voltage traces were digitized using an acquisition board (National Instruments, USA) controlled by IGOR software (WaveMetrics, USA) and the original data were saved for later analysis. The poststimulus time histograms (PSTHs) of responses were obtained for further analysis. The mean responses of each stimulus direction were used to draw the orientation tuning curve. The method for calculation of orientation bias (OB) and direction bias (DB) has been described elsewhere (Levick and Thibos, 1982; Schmolesky et al., 2000). These methods have been used in the calculation of the orientation sensitivities and direction sensitivities of the lateral geniculate nucleus (LGN) relay cells (Shou and Leventhal, 1989; Zhou et al., 1995) and the primary visual cortex (Hua et al., 2006). This is a global measure that is influenced by all of the data points on the tuning curve and was calculated as follows:

$$\mathrm{OB} = \left| \frac{\Sigma_k R_k e^{i2\theta_k}}{\Sigma_k R_k} \right|$$

$$\mathrm{DB} = \left| \frac{\Sigma_k R_k e^{i\theta_k}}{\Sigma_k R_k} \right|$$

where R_k is the mean spike rate in response to a drifting grating with orientation θ_k (in radians). OB, which averages the responses for the two directions of motion at each orientation and is quite robust in comparison to noise in the data, provides a bounded range from 0 to 1, with 0 indicating complete insensitivity to orientation and 1 corresponding to response at only one orientation. A cell with bias ≥0.1 was considered modestly biased and a cell with bias ≥0.2 was considered strongly biased for orientation or direction (Hua et al., 2006).

In principle, OB could be affected by bandwidth and orthogonal/optimal response independently (Ringach et al., 2002). Thus, for a more thorough investigation, the orientation-tuning curves of strongly orientation-biased cells were fitted to a von Mises distribution

$$R = R_0 + R_{max} exp\left\{k\left[\cos 2\left(\mathrm{Ori} - \mathrm{Ori_p}\right) - 1\right]\right\} \quad (1)$$

where R represents the response of the cell as a function of orientation (Ori), and $R_{\max}$, R_0, $\mathrm{Ori_p}$ and k are free parameters (Swindale, 1998). The preferred orientation was defined as the peak of the fitted function ($\mathrm{Ori_p}$). Width at half-height (WHH) of the fitted function was used to describe the tuning width, which was calculated as follows:

$$\mathrm{WHH} = \arccos[(\ln 0.5 + k) / k] \quad (2)$$

To investigate the effects of acute alcohol exposure on the ratio of the optimal and orthogonal orientation, the orientation-specificity index (OSI) (Wolf et al., 1986) was calculated as follows:

$$\mathrm{OSI}(\%) = \left(1 - \frac{\text{orthogonal response}}{\text{optimal response}}\right) \times 100 \quad (3)$$

OSI ranges from 0% to 100%, with larger values indicating greater difference between orthogonal and optimal responses.

A cell's signal-to-noise ratio was defined as the ratio between the cell's visually evoked response to the optimal stimulus and the cell's spontaneous response (Ego-Stengel et al., 2002). To avoid data skewing or overestimation, all spontaneous activities below 1 spike per second were set equal to 1 spike per second for signal-to-noise analysis. The spontaneous activity was subtracted from the stimulus evoked response before OB, DB and signal-to-noise ratio analysis. We used a simple and objective method to classify cells as simple or

complex (Skottun et al., 1991). The ratio of the first Fourier component (FFT1) to the mean component (FFT0) of response to a neuron's optimal drifting sinusoidal grating provides a measure of the relative response modulation. When the ratio is above 1, the neuron is classified as a simple cell. If the ratio is below 1, it is classified as a complex cell (Skottun et al., 1991).

Data are expressed as mean ± standard error of the mean (SEM). Differences between groups were assessed with one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison tests. Repeated measures one-way ANOVA followed by Dunnett's multiple comparison test was used in the investigation of strongly orientation selective cells because measurements were taken form the same neuron following treatments with saline and with alcohol. Correlations were evaluated using the Pearson correlation coefficient r. Pairwise comparisons were done with the Wilcoxon matched-pairs signed-ranks test. Differences were considered significant at the level of $P<0.05$ for all tests.

Alcohol administration and evaluation. Alcohol was administered intravenously i.v. as a 20% (vol./vol.) saline solution via a syringe at a dose levels of 0.5, 1, or 2 g/kg to generate a series of blood alcohol concentrations. Several factors including the rate of consumption, the amount of alcohol, and the individual differences in metabolism and elimination, could affect the eventual observed blood alcohol level at the time of each electrophysiological recording. Thus, the dose of alcohol administered might not serve as a stable index to assess the actual effect of alcohol. In our experiment, samples of expired air were taken simultaneously with each recording, to estimate the alcohol level by detecting the breath alcohol concentration (BRAC) using a breath analyzer (Alcotest 6510, Dräger, Germany). We did not evaluate the blood alcohol level directly because the physical condition of the animal might be influenced by taking blood samples frequently. Figs. 1A–C illustrate the schematic diagram of a representative electrophysiological recording procedure in our experiment.

Results

The BRAC rose rapidly after the administration of ethanol and reached a maximum in 30–60 min. A dose of 0.5 g/kg yielded a peak BRAC value of about 100 μg/L and a dose of 2 g/kg yielded a peak BRAC value of about 400 μg/L (Fig. 1D). There was a linear relationship between the dose of ethanol and the maximal BRAC value, in agreement with McKee et al., 2006. After reaching a maximum peak level, BRAC declined at a constant rate, also consistent with previous reports (Jones, 1984). The clearance of alcohol was dose-dependent and took 4–10 hours.

Response properties of A17 cells

Cells successfully recorded were assigned to one of three experimental treatment categories (TC) on the basis of the BRAC value: control treatment category (control TC, BRAC = 0, $n=60$); low alcohol concentration treatment category (low TC, BRAC < 100 μg/L, equivalent dose <0.5 g/kg, $n=66$); and high alcohol concentration treatment category (high TC, BRAC > 200 μg/L, equivalent dose >1 g/kg, $n=92$). No systematic differences in the effects of alcohol was observed for cells classified as simple or complex, and so the results from both types of cells are combined.

We compared the response properties of neurons in the three treatment categories. One-way ANOVA indicated that the acute alcohol exposure resulted in a significant reduction in various response properties of A17 neurons, including spontaneous activity (Fig. 2A, $P<0.05$), peak response (Fig. 2B, $P<0.05$), signal-to-noise ratio (Fig. 2C, $P<0.05$), and orientation selectivity (Fig. 2D, $P<0.05$), but the direction selectivity was not affected by alcohol significantly (Fig. 2E, $P=0.16$). To determine whether the suppressive effect alcohol was only exhibited in the optimal orientations or occurred across all orientations, we also compared the average response across all orientations of A17 neurons in the three TCs. The average response was also affected by alcohol (Fig. 2F, $P<0.05$). Further analysis using Dunnett's multiple comparison tests indicated that despite the overall tendency of a decreased response, we did not find significant differences between the low TC and the control TC in the spontaneous activity (3.58 ± 0.28 vs 3.71 ± 0.35 spikes/s, $P=0.39$), the peak responses (25.49 ± 1.87 vs 29.50 ± 1.93 spikes/s, $P=0.16$), the signal-to-noise ratio (8.68 ± 0.63 vs 10.34 ± 1.07, $P=0.16$), the orientation selectivity (0.29 ± 0.02 vs 0.33 ± 0.02, $P=0.34$) or the average response (9.39 ± 0.72 vs 10.68 ± 0.80 spikes/s, $P=0.23$). However, cells in the high alcohol concentration treatment category showed significantly decreased spontaneous activity (2.80 ± 0.23 vs 3.71 ± 0.35 spikes/s, $P<0.05$), peak responses (19.45 ± 1.84 vs 29.50 ± 1.93 spikes/s, $P<0.01$), signal-to-noise ratio (6.72 ± 0.64 vs 10.34 ± 1.07, $P<0.01$), orientation selectivity (0.22 ± 0.03 vs 0.33 ± 0.02, $P<0.05$) and average response (8.16 ± 0.94 vs 10.68 ± 0.80 spikes/s,

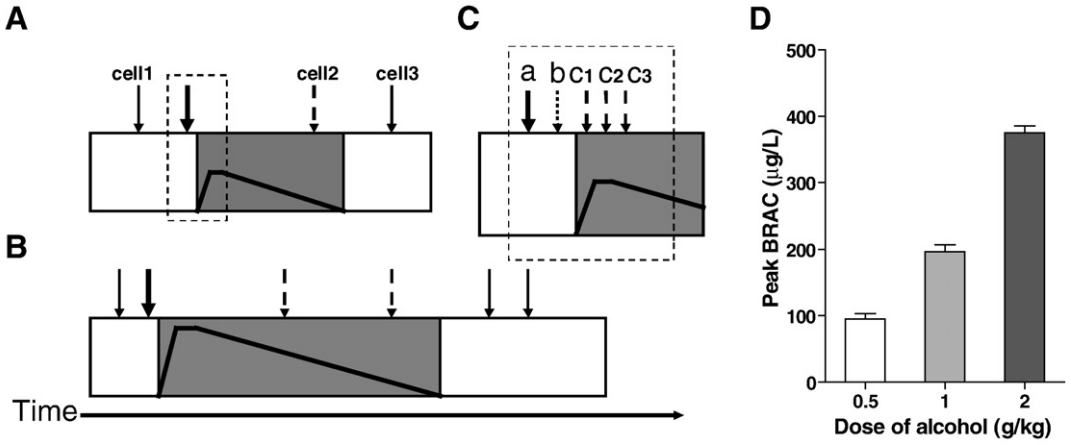

Fig. 1. Outline of study design consisting of several electrophysiological recordings before (white box) and during an acute alcohol administration (grey box) in two representative penetrations. Boxes are not accurately proportional to the real amount of time. The curves in grey boxes indicate the absorption and elimination period of alcohol. (A) Cell 1 and cell 3 were taken as the control group data (BRAC = 0); cell 2 was classified into the low alcohol group (BRAC < 100 μg/L). (B) In another penetration, a higher dose of alcohol was administered and thus led to a correspondingly longer elimination period. (C) A detailed illustration for the record procedure denoted by the dashed box in A. After a strongly orientation-biased cell was isolated and recorded (arrow a), repeated recordings were made after saline administration (arrow b) and alcohol administration (arrow c1, c2, c3). Data obtained in this section were also categorized into control treatment condition (b) and alcohol treatment condition (c1, c2, c3), respectively. (D) The relationship between the peak BRAC and the dose of alcohol administrated.

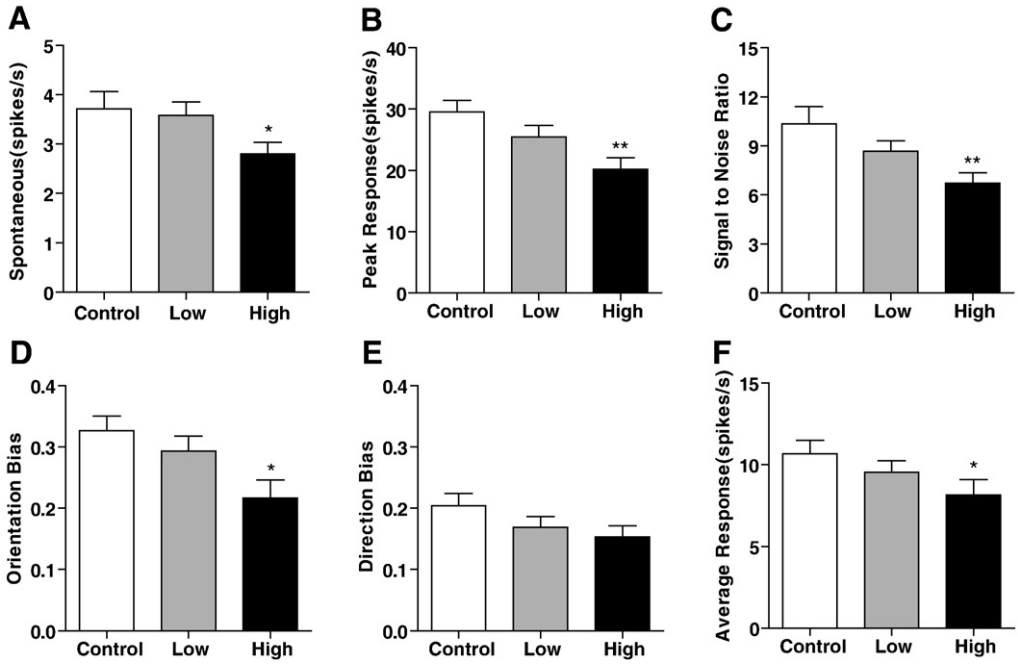

Fig. 2. Effects of alcohol on various response properties of A17 cells in the control treatment category (TC), the low concentration TC and the high concentration TC. One-way ANOVA indicates that alcohol has significant effect on the (A) spontaneous activity ($P<0.05$), (B) peak response ($P<0.05$), (C) signal-to-noise ratio ($P<0.05$), (D) orientation bias ($P<0.05$), and (F) average response ($P<0.05$). No significant difference was found in direction selectivity (one-way ANOVA, $P=0.16$) (E). (Error bars denote SE; * and ** denote the statistical difference between the control group and the high concentration group by Dunnett's multiple comparison tests. *$P<0.05$, **$P<0.01$.)

$P<0.05$) compared to the control TC (Figs. 2A–D, F). Our results therefore suggested that the effect of alcohol was dose-dependent, since significant changes in response properties were observed only in the high TC compared to the control TC.

Effect on orientation tuning profiles of strongly orientation-biased A17 cells

To further investigate the mechanism of reduced orientation selectivity induced by acute alcohol exposure, a total of 24 strongly orientation selective cells (OB≥0.2) were recorded both before and after alcohol administration. Half of them (12/24) were also strongly direction selective (DB≥0.2). Each cell was recorded twice before alcohol administration: the first recording was made normally and the second recording was made after administration of a volume of saline equivalent to the volume of alcohol that was administered later. After alcohol administration, each cell was recorded several times at intervals of 15–30 minutes. The concentration of alcohol was also evaluated simultaneously with each recording, and the data of individual A17 neurons under the peak BRAC were combined.

We combined the data because the primary concern in this part of the experiment was the substantial influence of alcohol on the orientation tuning curve irrespective of whether the effect was dose-dependent. Another reason for combining the data was the limited number of samples due to the relatively long elimination period after each alcohol administration.

Figs. 3A–C illustrate the orientation-selective response curves of a typical neuron in conditions of control (untreated), saline administration, and alcohol administration (at peak concentration). The orientation-tuning profiles of this cell were fit to a von Mises distribution (shown in Fig. 3D) as defined in Eq. (1) (see Materials and methods). It could be seen that there was a decrease in response at the optimal orientation and a broadening of tuning in the condition of alcohol administration, compared to the untreated and saline administration.

Repeated measures one-way ANOVA followed by Dunnett's multiple comparison test indicated that saline administration had no significant effect on the OB value (0.48 ± 0.04 vs 0.47 ± 0.03, $P=0.24$), while 75% of the cells (18/24) exhibited decreased orientation selectivity after alcohol administration (Fig. 4A). The averaged OB value was significantly decreased from 0.48 ± 0.04 to 0.37 ± 0.04 (Dunnett's multiple comparison test, $P<0.01$). It should be noted that the data obtained at relatively higher BRAC may make correspondingly larger contributions to the decrease of OB overall, due to the dose-dependent effect of alcohol.

Similarly, no significant difference was found in DB after saline administration (0.23 ± 0.03 vs 0.23 ± 0.03, Dunnett's multiple comparison test, $P=0.78$) (Fig. 4B). Although the direction selectivity could be affected after the administration of alcohol for some cells, the overall change in the DB values was not significant (from 0.23 ± 0.03 to 0.19 ± 0.02, Fig. 4B, Dunnett's multiple comparison test, $P=0.19$). Interestingly, the decrease of direction selectivity observed (from 0.38 ± 0.04 to 0.23 ± 0.03, Dunnett's multiple comparison test, $P<0.05$) in those strongly direction selective cells (DB≥0.2) was significant.

As mentioned in Materials and methods, OB could be affected by bandwidth and orthogonal/optimal response independently (Ringach et al., 2002). Thus, OB analysis cannot tell us whether the changes of orientation selectivity should be attributed to changes of bandwidth or orthogonal/optimal responses or both. To address this question, we studied the effects of acute alcohol exposure on both orientation bandwidth (measured as WHH) and orthogonal/optimal ratio (measured as OSI) of these strongly orientation-biased cells. Our results indicate that saline administration did not alter the OSI and WHH significantly (data not shown), while nearly three-quarters (19/24) of the cells showed a decreased OSI (Fig. 4C) and a similar portion (18/24) showed increased WHH (Fig. 4D) after the administration of alcohol. The mean OSI of the cells recorded was decreased significantly (from $79.9\pm2.9\%$ to $63.0\pm3.9\%$, Dunnett's multiple comparison test, $P<0.01$), and the mean WHH was increased significantly (from $45.1^\circ\pm3.9^\circ$ to $59.7^\circ\pm3.8^\circ$, Dunnett's multiple comparison test, $P<0.05$).

These results suggested that the changes of orientation selectivity after alcohol administration were due to changes of both bandwidth and orthogonal/optimal responses. As shown in Fig. 4E, more than half the cells (14/24) had values located in the top-left quadrant, a

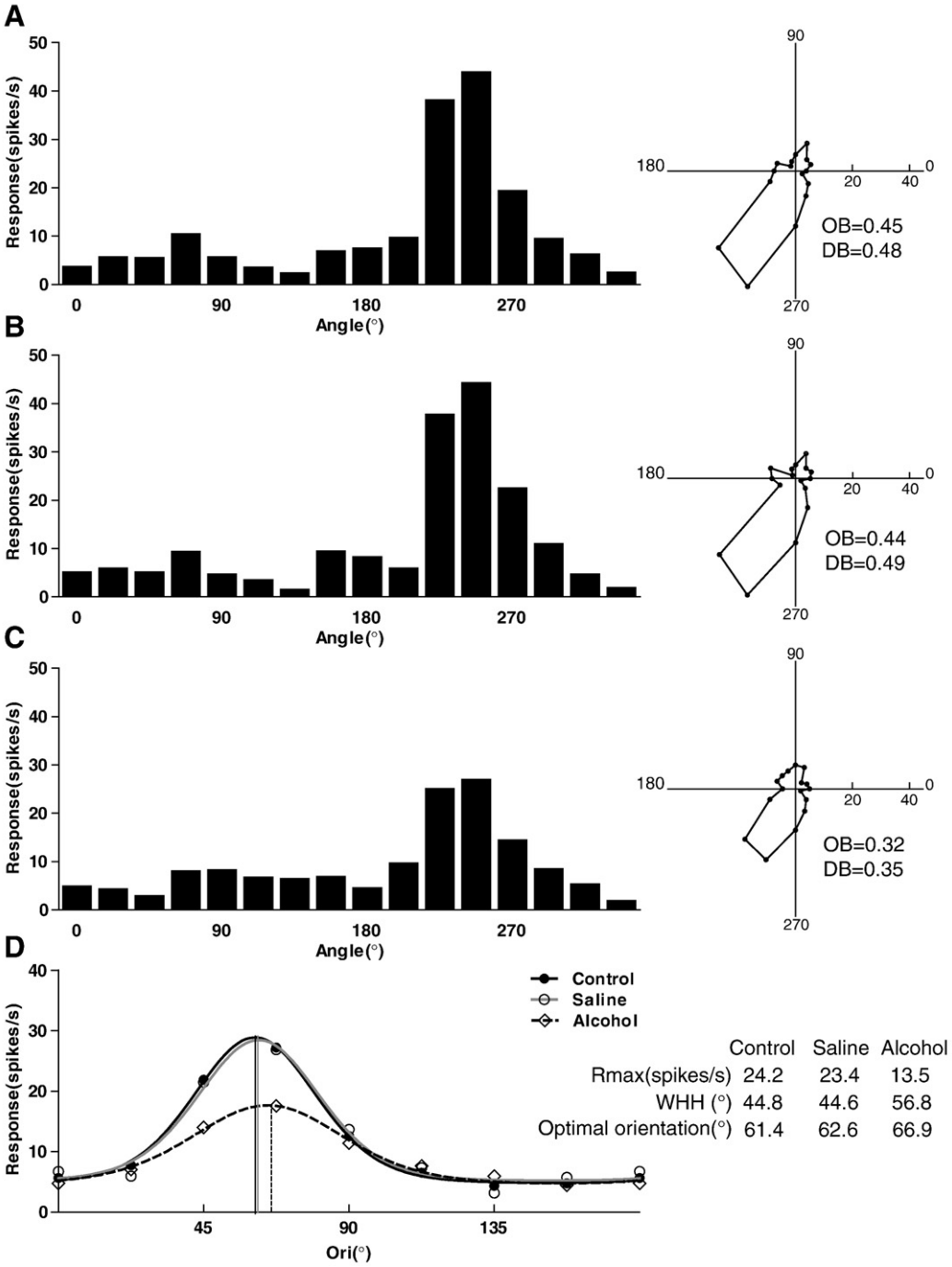

Fig. 3. Orientation tuning curves of a representative strongly orientation biased A17 cell in conditions of (A) control (untreated), (B) saline administration, and (C) alcohol administration (at a BRAC of 210 μg/L). (D) Tuning curves of A–C were all fitted with a von Mises distribution.

decrease of OSI being associated with an increase of WHH, clearly indicating a flattened tuning curve for these A17 neurons after alcohol administration. Another nine cells showed a decrease or no change in WHH or OSI, or an increase in the two parameters, which might influence the tuning curve in an unpredictable way. In fact, about half of the cells (4/9) showed decreased OB (denoted by filled triangles in Fig. 4E). Only one cell showed a clearly decreased WHH accompanied by an increase in OSI (bottom-right quadrant of Fig. 4E), which would result in an increased OB. For the whole sample, the changes in these two parameters were not correlated (Fig. 4E, Pearson $r = -0.19$, $P = 0.37$).

The alteration of the excitatory/inhibitory balance could influence both the peak response and the orientation selectivity. We thus employed an index to simply measure the degree of alcohol-induced suppression during alcohol administration, by calculating the relative change in peak response of individual cells after the alcohol administration. Overall most of the cells (19/24) are located in the bottom left quadrant of the Fig. 4F, showing a decrease of OB being associated with a decrease of peak response after alcohol administration. Only one cell showed substantially increased OB among the 20 cells that showed decreased peak response (located in the left-hand quadrants) after alcohol administration, indicating that the reduction in response to the optimal stimulus (represented by peak response) might be predominantly responsible for the alcohol-related deficit in orientation selectivity of A17 cells. A strong correlation was observed (Pearson $r = 0.42$, $P < 0.05$) when we examined the relationship

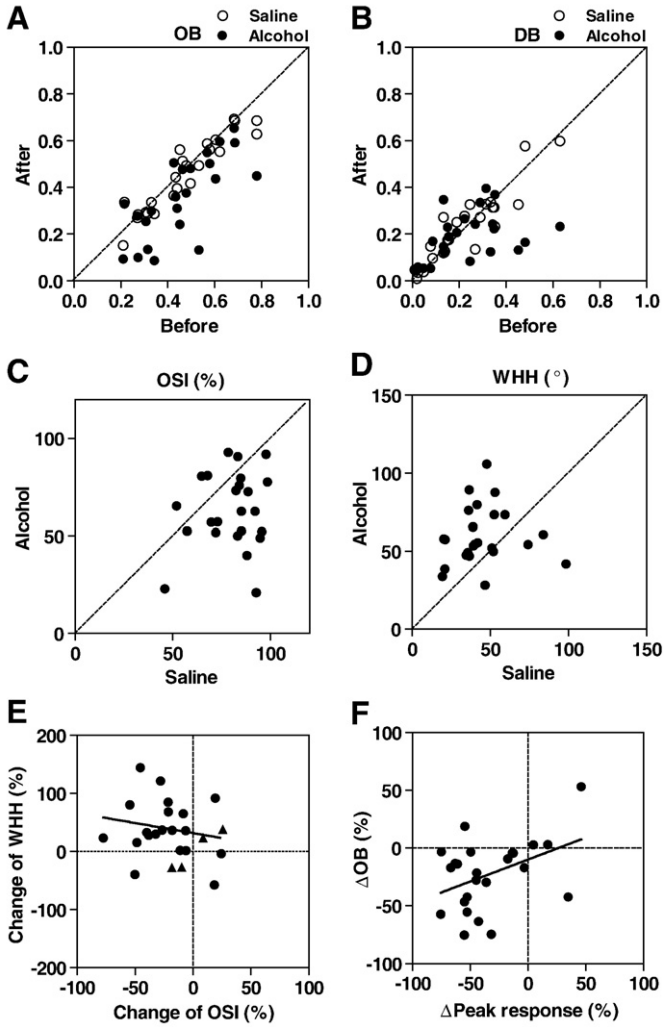

Fig. 4. Effects of alcohol on the orientation/direction selectivity and tuning curve profiles of strongly orientation selective cells. (A) Orientation bias (OB) of the cells after saline and alcohol administration was plotted separately. Most of the data points were located below the diagonal line (dashed) after alcohol administration (solid circle), while all the data points for the same population after saline administration (open circle) located close to the diagonal line. (B) Data points of direction bias (DB) were also located near the diagonal line after saline administration. In the condition of saline administration, the data points were more widely scattered. Overall there was no significant change in DB after alcohol administration ($P=0.19$), whereas those strongly direction selective cells (DB≥0.2) exhibited significantly decreased DB on average ($P<0.05$). (C) For most of cells, acute alcohol exposure resulted in a decrease in the optimal/orthogonal responses (the orientation specificity index, OSI, see Materials and methods) and most of the data points fall below the diagonal line (dashed). (D) For most of cells, acute alcohol exposure resulted in an increase in the width at the half height (WHH) of the orientation tuning curve and most of the data points fall above the diagonal line (dashed). (E) Relationship between a change in the OSI and that in the WHH. No correlation was found ($P=0.37$). (F) A strong correlation (Pearson $r=0.42$, $P<0.05$) was found between the change in the response to optimal orientation (peak response) and the change in the orientation selectivity (OB).

between the changes in peak response and the changes in OB for these cells.

Effect of alcohol on optimal orientation and direction

We calculated the optimal orientation and direction, both before and after acute alcohol administration. An interesting observation was that exposure to alcohol elicited a significant shift in optimal orientation and direction. The vertical lines in Fig. 3D indicate the cell's optimal orientation in different situations and reveal a small but clear shift in optimal orientation following acute alcohol administration. For most of the cells, the absolute shift in optimal orientation and direction was maximal within 30–60 min after alcohol administration, during which time the BRAC also attained the maximum level (a representative neuron is shown in Fig. 5A, data points at 0 min represent the shift after saline administration). The shift in the optimal orientation/direction appears to be dose-dependent because a strong correlation between the absolute shift magnitude and the alcohol concentration was observed in the optimal orientation (Fig. 5B, Pearson $r=0.42$, $P<0.001$) and in the optimal direction (Fig. 5B, Pearson $r=0.45$, $P<0.001$).

The absolute maximum shift of optimal orientation and direction induced by alcohol is plotted against that of saline in Fig. 5C. If alcohol had no effect on the optimal orientation/direction, the data points should locate near the broken diagonal line. However, our data showed that nearly all data points were above the diagonal line, which indicates that, alcohol induced a much greater shift in optimal orientation and direction compared to saline for individual cells. To investigate the significance, we calculated the difference between absolute shift in optimal orientation after alcohol administration and that after saline administration for each cell. It was significantly different from zero ($6.90°\pm2.67°$, Wilcoxon signed rank test, $P<0.01$).

Similar results were found for the optimal direction ($24.93°\pm4.90°$, Wilcoxon signed rank test, $P<0.0001$). In Fig. 5D, the maximum shift of optimal orientation was plotted against that of optimal direction for each cell. As is apparent in the figure, there was a strong correlation between them in the condition of alcohol administration (Pearson $r=0.57$, $P<0.01$), whereas no significant correlation was found in the condition of saline administration ($P>0.05$).

Discussion

This study provides evidence for an alcohol-induced decline in cortical cell function. Area 17 cells showed significantly decreased orientation selectivity accompanied by a shift of optimal orientation and direction after exposure to alcohol. A significant reduction in direction selectivity was also observed in strongly direction selective cells. The decreased signal-to-noise ratio induced by acute alcohol exposure indicated a degraded ability of 'drunk' cells to retrieve signals from noisy backgrounds. The effective concentration of alcohol observed in our study is not unusually high (200–400 μg/L in BRAC, which is equivalent to a blood alcohol level of approximately 0.04–0.08%, with a mean blood alcohol level of approximately 0.055%). Our findings were consistent with the notion that alcohol could elicit rather dramatic changes in the visual and ocular motor systems at a blood alcohol concentration as low as about 0.05% (Wilson and Mitchell, 1983).

Orientation selectivity, direction selectivity, and signal-to-noise ratio

The signals provided by individual neurons represent a fundamental medium of information transfer within the nervous system. For instance, Bradley et al. found that the best discrimination thresholds for orientation in the visual cortex of anesthetized cats were comparable with the known psychophysical performance of cats (Bradley et al., 1987). Similar results were found in alert rhesus monkeys (Vogels and Orban, 1990).

Humans perform poorly at tasks requiring orientation or pattern perception after acute alcohol consumption (Nicholson et al., 1995; Pearson and Timney, 1998; Pearson and Timney, 1999). These tasks presumably rely on the competence of orientation selective cells. Because A17/V1 is the first site where strong orientation selectivity is observed, losses at this site and/or the extrastriate cortex might partially mediate these perceptual declines. Theoretically, the alcohol-induced reduction in orientation selectivity, associated with the shift in optimal orientation of strongly orientation-biased A17 neurons, could impact the coding of orientation, consequently reducing the

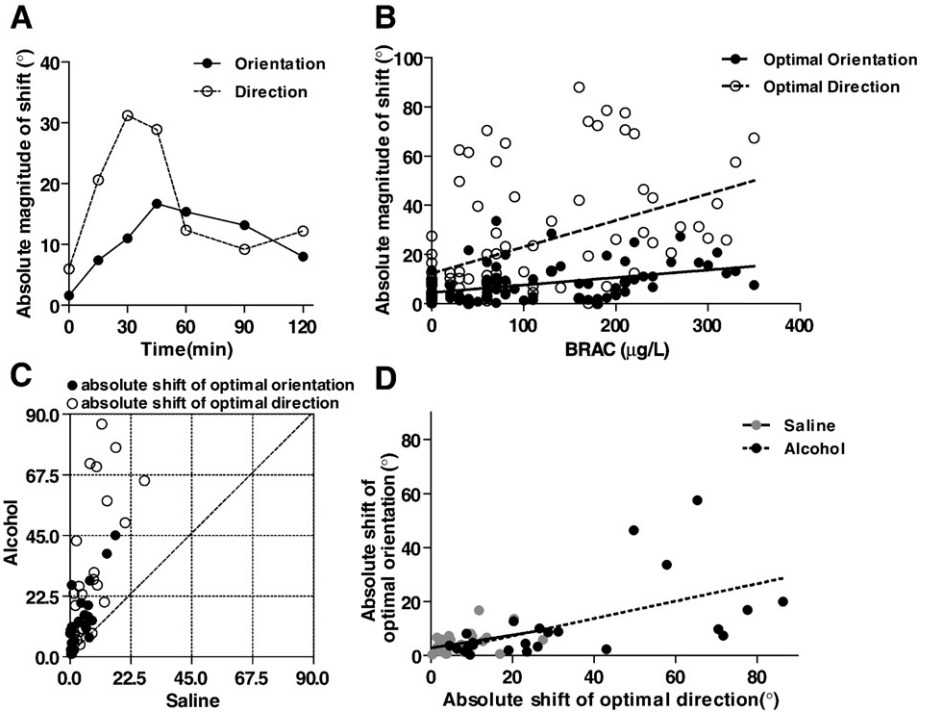

Fig. 5. Effects of alcohol on optimal orientation and direction of A17 neurons. (A) An example showing the shift of a cell's optimal orientation and direction after acute alcohol exposure, the points at 0 min in the graph indicate the shifts after saline administration. (B) Scatter plot of the absolute shift of optimal orientation/direction versus the alcohol concentration. The solid line represents the linear regression of the data for optimal orientation (Pearson $r=0.42$, $P<0.001$) and the dashed line for optimal direction (Pearson $r=0.45$, $P<0.001$). (C) A comparison of the absolute shift in optimal orientation/direction in the conditions of maximum alcohol concentration and saline administration. Each symbol represents the relationship for a single neuron. Nearly all of them are above the diagonal line (dashed). (D) For each cell, the maximum absolute shift of orientation was plotted against the absolute shift of direction. Black symbols correspond to the data in the condition of alcohol administration and the dashed line indicates the regression fit (Pearson $r=0.57$, $P<0.01$). Grey symbols correspond to the saline administration and no significant correlation was observed ($P>0.05$).

recognition of an object at the behavioral level, because the discrimination of orientation is required in the functional organization of form representations and shape integration (Wang and Hess, 2005; Kasai et al., 2007).

The selective decrease in the direction selectivity and the shift in optimal direction of those strongly direction-biased cells might result in a worsened recognition of motion. Our findings suggest an additional mechanism for the alcohol-related impairments in motion discrimination (Neill et al., 1991). In addition, the results of some studies suggest that the alcohol-related deficit in visual perception is likely to be enhanced under conditions where an object is moving rapidly. For example, an early study had demonstrated that alcohol could reduce the dynamic visual acuity, but not the static visual acuity (Adams et al., 1975). Static acuity is exclusively a function of various optical resolution factors of the eye, while dynamic visual acuity is the ability to discriminate detail in an object when there is relative movement between the observer and the object (Reading, 1972). Acute alcohol consumption was also found to significantly impair both static and dynamic contrast sensitivity, with a greater effect for moving targets (Nicholson et al., 1995). The visual impairments found in these two experiments were observed at a dose of about 1 g/kg and a BAC of 0.043%, respectively, which are comparable to the effective concentration observed here (slightly over 1 g/kg or 0.04% in BAC). Given that the moving gratings used in these studies required the subjects to make pursuit eye movements, which rely in part on motion detection, our results might provide an additional physiological explanation for the poorer performance at tasks requiring motion recognition.

In line with previous reports (Salamy and Williams, 1973; Neill et al., 1991; Perra et al., 2008), we found that acute administration of alcohol results in decreased stimulus driven and spontaneous activity. The proportionally greater decrease in peak response resulted in a reduced signal-to-noise ratio, indicating a reduced signaling capacity of A17 cells in general, which may be partially involved in the impaired information processing after the administration of alcohol (Koelega, 1995). Moreover, the decreased signal-to-noise ratio may be involved in the prolonged reaction time to simple stimuli, which has been observed at a comparable level of alcohol (0.05% in BAC) in psychophysical research (Tzambazis and Stough, 2000).

Mechanism consideration

Our findings suggest that functional changes of cortical neurons might underlie various visual perception impairments following acute alcohol consumption.

In this regard, Hubel and Wiesel proposed an elegantly simple model for the origin of cortical orientation selectivity that still serves as a central reference point. According to the model, simple cells in A17, the primary thalamo-recipient cells, become orientation selective by virtue of excitatory convergent input from lateral geniculate nucleus (LGN) neurons whose receptive fields are spatially organized (Hubel and Wiesel, 1962). However, there is evidence showing that intracortical inhibitory mechanisms contribute to the sharpening of orientation tuning functions (Sillito, 1975; Somers et al., 1995; Shapley et al., 2003). On the other hand, complex cells receive excitatory input from the LGN (Hoffman and Stone, 1971) or from other cortical cells (Gilbert and Wiesel, 1979) and the orientation tuning appears to be a product of the interaction of the excitatory and inhibitory inputs converging onto a given cell (Sillito, 1979).

Alcohol has been shown to interact with a number of excitatory and inhibitory neurotransmitters known to be involved in visual processing, including glutamate (Nie et al., 2000), γ-aminobutyric acid (GABA; Ticku and Mehta, 1995) and acetylcholine (Eckardt et al., 1998). One possible explanation for our finding is that alcohol alters the balance between excitatory and inhibitory processes.

Thalamocortical synapses are thought to be purely excitatory (Freund et al., 1989) and the predominant neurotransmitter involved in LGN feed-forward projection is glutamate (Bickle, 2001), which is an ubiquitous excitatory neurotransmitter in the cortex and is also used as the neurotransmitter in the excitatory interconnections among cortical cells (Miller et al., 1989). The glutamate system could be inhibited by alcohol through the direct action on the glutamate receptor (Harper and Matsumoto, 2005) and the inhibitory action on transmitter release via Ca^{2+} channel inhibition (Moriguchi et al., 2007). Thus, for a given cortical cell, the excitatory feed-forward input from LGN and/or excitatory input from other cortical cells could be reduced by alcohol. A decreased input from retina to LGN after administration of alcohol could also be involved, because the geniculate neurons and their strongest retinal inputs have very similar receptive fields (Reid and Shapley, 1992).

On the other hand, the dominant inhibitory neurotransmitter of the mammalian brain is GABA (Mody et al., 1994), which has been shown to play an important role in shaping cortical cell orientation tuning by suppressing the responses away from the optimal orientation (Ben-Yishai et al., 1995; Somers et al., 1995; Shapley et al., 2003). It has been reported that alcohol generally exhibits an enhanced action of GABA at GABAa receptors (Proctor et al., 1992), which is one of the most important target sites for the behavioral effects of ethanol (Moriguchi et al., 2007). Our results suggest that despite the effect of the enhanced GABA-mediated inhibition, the decreased excitatory input from LGN and/or other cortical cells may have a major role in reducing the orientation selectivity of A17 neurons in overall.

For those strongly orientation-biased cells, the decreased orientation selectivity might be attributed predominantly to the attenuated excitation, because highly orientation-selective cells were thought to have strong endogenous inhibition strength (Troyer et al., 1998), thus increased inhibition could not alter the orientation selectivity significantly (Li et al., 2008). The correlation between changes in OB and in peak response lends support to our hypothesis that the decreased excitatory inputs, which result in a reduction of the optimal response, may be largely responsible for the reduction in orientation selectivity.

The lack of a differential action of ethanol on simple cells and complex cells observed in our experiment may, to some extent, be due to the equal sensitivity of the two types of cells to glutamate and GABA (Wallingford et al., 1973), since many complex cells also receive direct LGN input (Hoffman and Stone, 1971), which could contribute in a significant way to their orientation tuning (Mel et al., 1998).

The orientation–tuning curve is regarded as providing the neural basis for behavioral performance in orientation discrimination (Moran and Desimone, 1985). Our results suggest that the changes of orientation selectivity during the administration of alcohol were due to the changes in both bandwidth and orthogonal/optimal responses. Our results also support the notion that OB could be affected independently by bandwidth and the orthogonal/optimal response (Ringach et al., 2002).

It should be noted that other factors, such as the excitatory lateral integration between cortical neurons, might be involved. For example, if the excitatory lateral connections were predominantly from neurons with similar preferred orientations, a reduction of their efficacy would result in reduced orientation tuning (as preferred orientation input might be relatively decreased). If, however, the lateral connections were mostly from neurons with different preferred orientations, a reduction of their efficacy would partially compensate for the reduction in orientation selectivity. Moreover, the alcohol-induced alteration of intracortical excitation between different orientation columns might also be capable of mediating the shift in optimal orientation, because the network mechanism of reorganizing the responses across a broad range of orientations was possibly through changes in the gain of local cortical circuits integrated by excitation and inhibition (Ben-Yishai et al., 1995; Somers et al., 1995). If the synaptic inputs from cells of different orientation columns connected to the recorded cell were influenced unequally by alcohol, the surrounding cells would exhibit different contributions to the tuning of the recorded cell, possibly causing a shift of the tuning curve as a result. For example, if a cell normally sensitive to $+10°$ becomes most sensitive to 0°—induced by altered inputs from a large pool of surrounded cells—then a 0°(vertical) test stimulus will now be seen at $+10°$ because $+10°$ is the orientation normally signaled when that cell is the most active one. Hence, a shift in optimal orientation would be observed.

Many cells in early visual cortex processing are simultaneously tuned to both orientation and direction (Hubel and Wiesel, 1968). The origin of cortical direction selectivity involves a mechanism similar to that of orientation selectivity in terms of the balance of excitation and inhibition. Some models predict that excitation would be tuned for the preferred direction (McLean and Palmer, 1989; DeAngelis et al., 1993), whereas others predicts that only the interaction of inhibition and excitation could be tuned for motion direction. A recent study (Priebe and Ferster, 2005) suggested that excitation would play a more important role in direction selectivity. Despite the discrepancy among these models, the enhanced inhibition and attenuated excitation induced by alcohol might result in a decreased response on preferred direction and consequently lead to a decreased DB. However, considering that the cells in A17 exhibited much lower averaged direction selectivity than orientation selectivity, the decrease of DB induced by the suppressed response to optimal stimuli was presumably less notable than that of OB. The direction selectivity for the whole population thus exhibited a tendency of decreased selectivity (though not significant, Fig. 2B). In other words, alcohol did not affect DB significantly because values were already low. In contrast, for those strongly direction selective neurons ($DB \geq 0.2$), the attenuated excitation might exhibit a more marked effect, leading to a significant reduction in DB.

It has been reported that direction-selective A17 cells are tuned to orthogonal orientation and motion axes (Albright, 1984), which leaves open the possibility that the alcohol-induced shift in the optimal direction of A17 cells we observed here was a simple consequence of the shift in the preferred orientation, even if there was no direct effect of alcohol. However, the lack of a consistent relationship between the shift in the optimal orientation and direction indicates that the shift in the optimal direction of A17 cells we observed here is mainly the result of the asymmetric changes in excitatory inputs from a large pool of surrounded cells, as well as the intracortical interactions.

The enhanced inhibition and attenuated excitation induced by alcohol might be responsible also for the decreased spontaneous activity, peak response and average response, because the cellular mechanisms regulating neuronal activity require coordinated excitatory and inhibitory synaptic inputs. The suppression of spontaneous activity could arise when ethanol inhibited excitatory glutamatergic activity and enhanced inhibitory GABAergic activity. The reduction of visual evoked responses might result from tonic hyperpolarization of the membrane potential (Cardin et al., 2007), due possibly to slow hyperpolarizing Ca^{2+}-activated potassium channels (Sanchez-Vives et al., 2000), which could be effected by alcohol (Brodie et al., 2007). In our data, the peak response in the high alcohol concentration TC decreased by 34.2% compared to the control, exceeding the reduction in the spontaneous activity (22.9%). Thus, the signal-to-noise ratio, which relates to the detection capability of sensory neurons, is significantly decreased in the high alcohol TC. The result that high-concentration alcohol significantly suppressed the average response (across all orientations) by 23.6% (Fig. 2F), which is also smaller than the reduction of peak response, further indicates that the more significant decreased responsiveness to optimal orientations appears to be an important mechanism mediating the reduction in stimulus selectivity.

We focus here mainly on glutamate and GABA because they are the most important excitatory and inhibitory neurotransmitters in the central nervous system. Alcohol affects many other neurotransmitters in the cortex as well: for example, acetylcholine, which has been suggested to play a role in the influence of alcohol on the visual system (Sillito and Kemp, 1983), might be involved. However, literature dealing with the effect of acetylcholine on orientation tuning functions and the signal-to-noise ratio of cortical cells is inconsistent with each other (Sillito and Kemp, 1983; Zinke et al., 2006). Moreover, a psychophysical study suggested that alcohol might affect other mechanisms that compensate for the effects of alcohol on acetylcholine in the visual system (Pearson and Timney, 1999). This could be an additional explanation for the lack of effect of acetylcholine on neuronal responsiveness in a large proportion of cortical cells observed in an electrophysiological study (Zinke et al., 2006).

Thus, we believe that the effect of alcohol on the acetylcholine did not play a major role in our observed results. Of course other neuron transmitters such as serotonin, dopamine, and glycine may also be affected by alcohol (Carmichael and Israel, 1975; Ye et al., 2001) and hence influence the intracortical excitation-inhibition balance, and therefore need to be studied independently.

Effect of acute tolerance

Acute tolerance to alcohol could be present in our experiment, because it can occur within a single administration (Tabakoff et al., 1986), although tolerance to most effects of alcohol generally develop over time and over several administrations of alcohol. Acute alcohol tolerance refers to the observation of reduced impairment at a given blood alcohol concentration on the descending versus ascending limb of the blood alcohol curve (Hiltunen and Jarbe, 1990). With regards to the acute alcohol tolerance, population data for group comparison (demonstrated in Fig. 2 and Fig. 4) were collected either at the peak BRAC or during the elimination period after each administration of alcohol (see Fig. 1 in Materials and methods). In other words, if problems related to acute tolerance significantly affected these results, then our results would underestimate the effects of alcohol on A17 cells.

The results shown in Fig. 5B must be taken into account when considering the possible influence of acute alcohol tolerance, because the data were lumped based on BRAC without regards to whether they were within the ascending or the descending limb. We thus compared the data for the same cells at the equivalent BRAC on the ascending and the descending limb of the curve. No significant difference was found either in the shift of optimal orientation, or in the shift of optimal direction ($n=9$, Wilcoxon signed rank test, $P=0.62$ and $P=0.33$, respectively).

Effects of anesthesia

Ketamine was only used to maintain anesthesia during the cannulation surgery before our electrophysiological recording. It did not appear to suppress the excitability of cortical neurons (Kalkman et al., 1994) and was considered well suited for both behavioral and electrophysiological investigations into mechanisms of visual processing (Leopold et al., 2002).

The electrophysiological recordings were performed under urethane anaesthesia, which was considered suitable (or, in any case, better suited than that produced by other anesthetics) for physiopharmacological investigations concerning GABAergic neurotransmission and its modulation by drugs (Maggi and Meli, 1986), due to its modest effects on multiple neurotransmitter-gated ion channels, especially, a minimal effect on GABAergic neurotransmission at a clinical concentration (Evans and Smith, 1982; Garrett and Gan, 1998). Urethane has been widely used as an anesthetic agent in studies of the effect of ethanol on neuronal activity of the central nucleus of the amygdala (Naylor et al., 2001), the basolateral amygdala projection neurons (Perra et al., 2008) and the prefrontal cortex neurons of rats (Tu et al., 2007).

However, it is not easy to exclude a combined effect of alcohol and urethane in our *in vivo* experiment using visual stimuli due to the similar spectrum of action on ion channels between alcohol and urethane (Hara and Harris, 2002). It is also true that alcohol may increase the systemic distribution of urethane by decreasing its first-pass clearance (Beland et al., 2005). In other words, alcohol may potentiate the effects of urethane during the experiments on urethane-anesthetized animals. However, our earlier study demonstrated that during the experiments on urethane-anesthetized cats, giving as much as four times the minimum level of general anesthesia or paralytic required to anesthetize or paralyze cat does not alter the degree of selectivity for orientation and direction that A17 cells exhibit (Hua et al., 2006). Moreover, the shift in optimal orientation and direction observed in our experiment is most likely not the result of the effects of urethane, since urethane exhibits no significant effect on the receptive field of visual cortical cells (Sceniak and Maciver, 2006). We thus believe that the effects of anesthesia on the results of this study should be at most minor. Given that, depending on the level of anesthesia, urethane may produce modest or marked effects on multiple neurotransmitter systems (Hara and Harris, 2002), confirmation of the results in the present study may require unanesthetized and freely moving animal models.

In summary, the present study demonstrates that acute alcohol exposure suppresses spontaneous activity and the visually evoked response, and alters the orientation/direction selectivity of A17 neurons. Our findings might provide a neurobiological substrate for some types of visual deficits that result from acute alcohol consumption. Though additional pharmacological experiments need to be done to confirm the precise cellular mechanisms, it appears that alcohol-induced attenuation in excitatory system might play a predominant role in mediating such changes in neuronal activity.

Conflict of interest statement

All authors declare that they have no conflicts of interest.

Acknowledgments

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