

# Characterization of the acute effects of alcohol on asymmetry of inferior frontal cortex activity during a Go/No-Go task using functional near-infrared spectroscopy

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## Abstract

**Rationale** Successful response inhibition is associated with right-lateralized inferior frontal cortex (IFC) activity, and alcohol impairs this inhibitory control, thereby enhancing false-alarm responses in the Go/No-Go task. However, the neural correlates of effect of alcohol on response inhibition remain unclear.

**Objective** This study characterized the acute effects of alcohol on IFC activity during Go/No-Go tasks using near-infrared spectroscopy (NIRS).

**Methods** Thirty-two subjects visited our laboratory twice: once for alcohol intake and once for placebo intake. On each visit, subjects performed Go/No-Go tasks immediately before and 10 min after intake of the alcohol or placebo. NIRS was used to evaluate IFC activity measured during Go/No-Go tasks.

**Results** Alcohol significantly enhanced false-alarm responses in No-Go trials. NIRS analysis showed that IFC activity was greater in the right hemisphere than in the left hemisphere prior to alcohol or placebo intake. This right hemispheric superiority was eliminated in response to alcohol but not in response to placebo. Correlation analysis

showed that subjects with right-lateralized IFC activity made fewer false-alarm responses in No-Go trials and that alcohol-induced inhibition of hemispheric IFC asymmetry resulted in higher false-alarm rates.

**Conclusion** These findings suggest that the right IFC may mediate the acute effects of alcohol on inhibitory control. When the alcohol impairs the right IFC activity, subjects cannot inhibit the pre-potent responses for No-Go trials, resulting in enhanced false-alarm responses. Thus, this study successfully demonstrated the neural correlates of the alcohol effect in the right IFC activity during inhibitory control processes.

**Keywords** Alcohol · Response inhibition · Inferior frontal cortex · Near-infrared spectroscopy · Go/No-Go task · Hemispheric asymmetry reduction

Alcohol impairs inhibitory control of behavioral responses that underlie various impulsive behaviors, including aggression, suicide, risky driving, and other socially inappropriate behaviors (Barkataki et al. 2005; Dougherty et al. 2008; Fillmore et al. 2008, 2009). Experimental assessments of response inhibition are often conducted using the Go/No-Go task, in which subjects are required to perform timed responses for Go trials (e.g., pressing a button in response to the letter A) and to inhibit responses for No-Go trials (e.g., refraining from pressing a button in response to the letter B). During a testing session, No-Go trials are typically given less frequency than Go trials in order to enhance the pre-potent response tendency during the task. Previous behavioral studies demonstrated that alcohol administration enhanced false-alarm responses to No-Go trials (Field et al. 2010; Fillmore et al. 2009; Ostling and Fillmore 2010).

Neuroimaging studies of response inhibition have suggested that the activity of right-lateralized inferior frontal cortex (IFC) is critical for the inhibitory functions (Aron et al. 2004; Bunge and Wright 2007; Rubia et al.

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2001). For example, successful response inhibition was associated with right IFC activity in the Go/No-Go task (Chikazoe et al. 2007; Herrmann et al. 2005), and right IFC activation was also enhanced by the task-set switching paradigm in which subjects were instructed to change from one task to another (Cools et al. 2002; Xue et al. 2008). Further, right IFC activity was associated with successful performance of belief-bias reasoning tasks in which subjects must inhibit automatic heuristic thinking (Tsujii et al. 2010a, b; Tsujii and Watanabe 2009, 2010).

What is unknown is how alcohol could influence the right-lateralized IFC activities associated with response inhibition. The present study thus examined the acute alcohol effect on the IFC activities during the Go/No-Go task using near-infrared spectroscopy (NIRS). NIRS is a relatively new imaging technique for investigating cortical hemodynamic responses by measuring changes in the attenuation of near-infrared light passing through tissue. Since oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) have different absorption spectra in the infrared range, changes in oxy-Hb and deoxy-Hb can be calculated by detecting infrared light at different wavelengths on the skull. In general, enhanced oxy-Hb and reduced deoxy-Hb are associated with regional cortical activation (Obrig et al. 2002). NIRS is noninvasive, is robust against body movement, and has been validated as a suitable technique for investigating neural mechanisms in psychological experiments.

In the present study, we hypothesized that alcohol would reduce the right-lateralized IFC activities, enhancing the false-alarm responses to No-Go trials. Reduced right-lateralized IFC activity is associated with impaired behavioral performance of inhibitory control (Rubia et al. 1999, 2001, 2005, 2007), and alcohol reduces the hemispheric asymmetry in cortical responses, thereby impairing behavioral performance in several cognitive tasks (Soderlund et al. 2007; Wendt and Risberg 1994, 2001; Wendt et al. 1994). These observations encouraged us to predict that alcohol would reduce the hemispheric asymmetry in IFC activation, impairing response inhibition performance in the Go/No-Go task.

## Methods

### Subjects

Subjects were 32 healthy Japanese volunteers (17 female, 15 male) ranging in age from 21 to 38 years (age [mean±standard deviation], 28.19±5.05 years). The Edinburgh Handedness Inventory (Oldfield 1971) indicated that 29 of the subjects were right-handed. All subjects had normal or corrected-to-normal vision. Subjects completed questionnaires that provided demographic information, drug use history, and

physical and mental health status. All subjects were fasted for 3 h prior to the session and abstained from alcohol for 24 h prior to the session. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all protocols were approved by the Ethics Committee of Nihon University School of Medicine. Written informed consent was obtained from all subjects prior to enrolment in the study.

### General procedure and alcohol administration

The experiment was run individually. All subjects visited our laboratory twice: once for alcohol intake and once for placebo intake. On each visit, subjects performed Go/No-Go tasks immediately before and 10 min after intake of the alcohol or placebo. Alcohol was administered at a dose of 0.5 g/kg of body weight, mixed with orange juice (total amount=400 ml). Vodka (37.5% alcohol) was chosen because of its purity compared with other alcohol-containing beverages (Leake and Silverman 1971). The placebo drink was the same total volume of orange juice (400 ml), so that the visual appearance was quite similar between alcohol and placebo drinks. Total administration time was 7 min for both sessions. Subjects drank 200 ml in the first 3 min, took a 1-min break, and then drank the second 200 ml in the remaining 3 min.

An interval of at least 3 days was given between visits. The order of alcohol and placebo sessions was randomized to control for any task-learning effect or temporal variances in the NIRS measurement. Upon arrival to the laboratory, all subjects were first tested with a breath analyzer (SC-302, Central Automobile Products Ltd., Osaka, Japan) and found to be sober. Subjects then performed the Go/No-Go task for approximately 18 min, followed by alcohol or placebo administration over the next 7 min. Breath alcohol concentration (BrAC) was tested again 10 min after administration of alcohol or placebo (mean BrAC, 0.24±0.06 mg/L after alcohol intake), and the Go/No-Go task was performed again over approximately 18 min. During the Go/No-Go tasks, the activity of IFC was measured using NIRS.

### Go/No-Go task

For each visit, subjects performed the Go/No-Go task twice: once immediately before the administration session and once 10 min after the administration session. Completion of the Go/No-Go task required approximately 18 min. The task was operated using E-Prime 2.0 software (Psychology Software Tools, USA). In the Go/No-Go task, 10 test blocks were sandwiched between 11 baseline blocks. Each test block contained 10 Go trials (occurrence probability=62.5%) and six No-Go trials (occurrence probability=37.5%), while each

baseline block contained 16 Go trials but did not contain No-Go trials. In the test block, the Go and No-Go trials were presented in randomly intermixed order. Each block required approximately 45 s to complete. At the beginning of each block, a cue was presented for 5 s to indicate whether the coming block was test or baseline.

The beginning of each trial was signaled by the fixation cross that appeared in the center of the computer screen for 500 or 1,500 ms. In the Go trials, the letter “A” was presented immediately after the fixation cross, and the subjects were required to press a response button as fast and as accurately as possible. By contrast, a “B” followed the fixation cross in the No-Go trials. Subjects were told to inhibit their prepared response in the No-Go trials. Both stimuli were presented until subjects made a response or until 500 ms passed. The inter-stimulus interval was 1,500 ms. A practice session was given for each visit to familiarize the subjects with the task.

### NIRS recordings

During the Go/No-Go task, relative changes in oxy- and deoxy-Hb concentration values were measured in the bilateral IFC regions using a two-channel portable-type NIRS system (PNIRS-10, Hamamatsu Photonics K.K., Hamamatsu, Japan). This device uses near-infrared light at three wavelengths, ranging around  $735 \pm 15$ ,  $810 \pm 18$ , and  $850 \pm 20$  nm. The oxy-Hb and deoxy-Hb values were estimated from the detected changes of the near-infrared light using Modified Beer–Lambert Law (Delpy et al. 1988). Because the individual optical path length is unknown, the hemoglobin concentration value is not an absolute but a relative value; this value is expressed as a change from baseline concentration (a.u., arbitrary units). The sampling frequency was 10.2 Hz (97.8 ms/data). Moving average methods were used to cut the high-frequency noise. The moving average window was 31 data points, which corresponds to approximately 3,032 ms.

The flexible NIRS probe (P-Probe-1 M, Hamamatsu Photonics K.K., Hamamatsu, Japan) consisted of a LED emitter and a detector, separated by a distance of 30 mm. The detectors were always placed more laterally relative to the emitters on the subject’s forehead (see Fig. 2). The detectors were placed at the F7 position for left IFC measurements and at the F8 position for the right IFC measurements (international 10–20 system). The F7 and F8 roughly correspond to the inferior frontal gyrus (Homan et al. 1987; Okamoto et al. 2004; Jurcak et al. 2005, 2007). For some subjects, detectors could not be placed precisely at the F7 or F8 position because the subject’s hair interrupted precise measurements. In those cases, the detector position was moved more medially. Mean movement distances were 9.25 mm (SD=9.56 mm) for the left IFC and 9.38 mm (SD=9.24 mm) for the right IFC.

### Data analysis

For behavioral performance, the reaction time (RT) for Go trials and the false-alarm rates for No-Go trials in the test block were analyzed. Trials in which the RTs were not within the time range of the mean  $\pm 3$  SD were excluded from the RT analysis. Data were compared by two-way analysis of variance (ANOVA), with within-subject factors of drink type (alcohol, placebo) and test period (before, after).

For NIRS response, the mean oxy- and deoxy-Hb concentration change ( $\Delta$ oxy-Hb and  $\Delta$ deoxy-Hb) were analyzed during the time window from 0 s (trigger-point: start time of the test block) to 45 s. Baseline epochs were set for a pre-trigger of 20 s in the baseline block. The baseline corrected oxy- and deoxy-Hb waveforms were averaged over the 10 test blocks. For statistical analysis, mean  $\Delta$ oxy-Hb and  $\Delta$ deoxy-Hb values were tested by three-way ANOVA, with within-subject factors of drink type (alcohol, placebo), test period (before, after), and hemisphere (LH, RH). Because the second-order interactions were significant both for  $\Delta$ oxy-Hb ( $F(1, 31)=4.19, p<.05$ ) and for  $\Delta$ deoxy-Hb ( $F(1, 31)=4.75, p<.05$ ), separate two-way ANOVAs were performed for each condition.

Finally, correlation analysis was performed between the right/left IFC activation and behavioral performance (false-alarm rates for No-Go trials and RTs for Go trials). The laterality index (LI) was used to represent the degree of hemispheric asymmetry of IFC activation and was calculated using the formula:

$$(R - L)/(R + L)$$

where R and L indicated  $\Delta$ oxy-Hb concentration values at the right and left IFC, respectively. Thus, high LI indicates strong right-lateralization of IFC activation. Furthermore, the effect of alcohol on the correlation between NIRS response and behavioral performance was assessed by subtracting values obtained after drinking placebo from those obtained after drinking alcohol.

## Results

### Behavioral performance

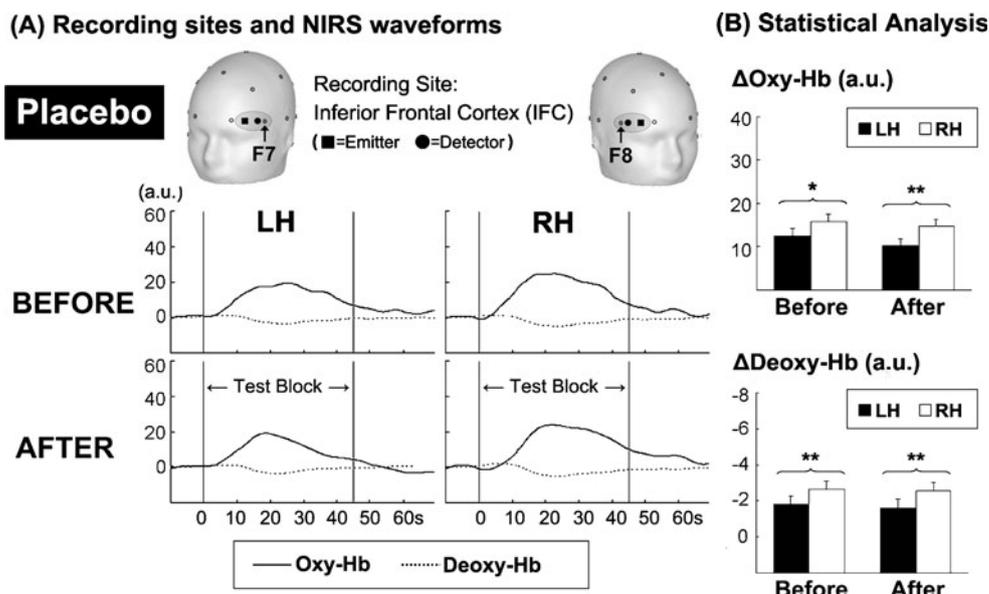
Figure 1a summarizes mean RTs for Go trials of each drink type. Two-way ANOVA revealed a significant drink type  $\times$  test period interaction ( $F(1, 31)=11.43, p<.01$ ), suggesting that alcohol significantly delayed responses when compared with placebo ( $F(1, 62)=15.27, p<.01$ ). However, there was no significant difference in response times between those same groups of volunteers before administration of alcohol or placebo ( $F(1, 62)=.06, p=.27$ ).

Figure 1b summarizes mean false-alarm rates for No-Go trials of each drink condition. Two-way ANOVA revealed a significant drink type  $\times$  test period interaction ( $F(1, 31)=9.16$ ,  $p<.01$ ), suggesting that alcohol significantly enhanced false-alarm rates when compared with placebo ( $F(1, 62)=16.83$ ,  $p<.01$ ). However, there was no significant difference in false-alarm rates between those same groups of volunteers before administration of alcohol and placebo ( $F(1, 62)=.06$ ,  $p=.81$ ).

NIRS response

Figure 2a

**Fig. 3** a Oxy- and deoxy-waveforms in the IFC region in the LH and RH during the Go/No-Go task before and after placebo administration. b The bar graphs represent the mean oxy- and deoxy-Hb values during the test blocks. The error bars represent the standard errors of oxy- and deoxy-Hb values. The Y-axis of the bar graph in reversed on  $\Delta$ deoxy-Hb, because reduced deoxy-Hb concentration values are generally associated with regional cortical activation. Significant comparisons are shown: \* $p < .05$ , \*\* $p < .01$



significant for either  $\Delta$ oxy-Hb ( $F(1, 31)=14.65, p < .01$ ) or  $\Delta$ deoxy-Hb ( $F(1, 32)=.06, p = .80$ ).

**Correlation analysis**

The relationships between behavioral performance and hemispheric IFC activity in the Go/No-Go task were analyzed. The correlation between the RTs for Go trials and the LI of IFC activities ( $r = -.18, p = .31$ ) was not significant (Fig. 4a). By contrast, there was a significant negative correlation between the false-alarm rates for No-Go trials and LI of IFC activities ( $r = -.37, p < .05$ ; Fig. 4b). Since high LI means that IFC activity is more right-lateralized, these findings indicate that subjects with right-lateralized IFC activity made fewer false-alarm responses for No-Go trials.

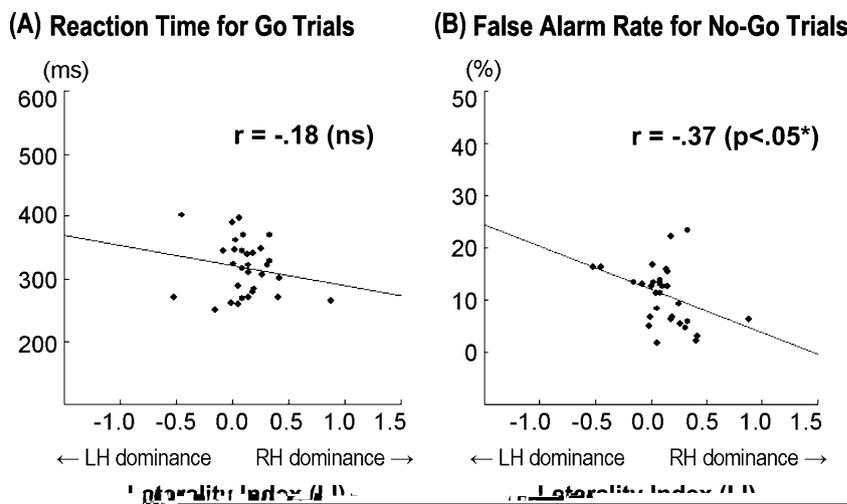
The relationship between alcohol effect, behavioral performance, and hemispheric IFC activity were assessed by subtracting values obtained after drinking placebo from those

obtained after drinking alcohol. The correlation between RTs for Go trials and LI of IFC activities was not significant ( $r = -.17, p = .35$ ; Fig. 5a), but there was a significant negative correlation between the false-alarm rates for No-Go trials and the LI of IFC activities ( $r = -.45, p < .01$ ; Fig. 5b). This means that subjects with alcohol-induced disruption of right lateralization of IFC activity had higher false-alarm rates for No-Go trials. By contrast, subjects in whom right lateralization remained high were able to maintain low false-alarm rates even after drinking alcohol.

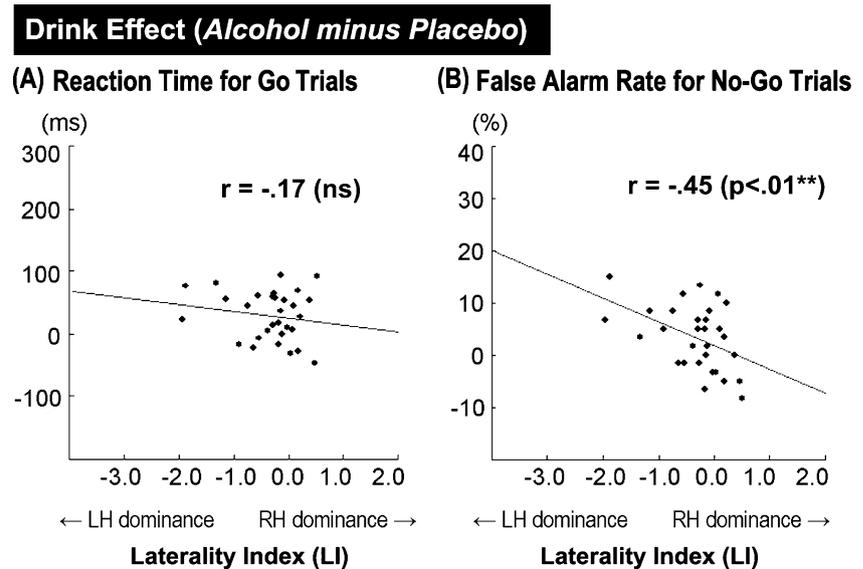
**Discussions**

The present study used NIRS to examine the effect of alcohol on hemispheric IFC activity during the Go/No-Go task. Subjects visited our laboratory twice: once for alcohol intake and once for placebo intake. On each visit, subjects

**Fig. 4** Relationships between behavioral performance and hemispheric lateralization of IFC activity in the Go/No-Go task. High laterality index indicates strong right lateralization of IFC activation. The laterality index was significantly correlated with false-alarm rates for No-Go trials (b) but not with reaction times for Go trials (a). Thus, subjects with right-lateralized IFC activity made fewer false-alarm responses in No-Go trials



**Fig. 5** Relationship of the effect of alcohol on behavioral performance and hemispheric lateralization of IFC activity was analyzed by subtracting values obtained after placebo intake from those obtained after alcohol intake. The laterality index was significantly correlated with false-alarm rates for No-Go trials (b) but not with reaction times for Go trials (a). Thus, subjects whose right-lateralization of IFC activity was disrupted by alcohol had higher false-alarm response rates, while subjects whose right lateralization remained high could maintain low false-alarm response rates



performed Go/No-Go tasks immediately before and 10 min after intake of the alcohol or placebo. We measured the hemispheric IFC activity during Go/No-Go tasks using NIRS. Here, we discuss the present findings in the following subsections: neural correlates of alcohol effect on response inhibition, hemispheric asymmetry reduction by alcohol consumption, and the limitations of this study.

#### Neural correlates of the effect of alcohol on response inhibition

The aim of this study was to examine the neural correlates of the effect of alcohol on response inhibition processes in the Go/No-Go task. Behavioral analysis found that alcohol administration enhanced the false-alarm responses for No-Go trials (Fig. 1), confirming previous behavioral findings (Fillmore et al. 2009). NIRS analysis showed that the alcohol consumption impaired right IFC activity without affecting left IFC activity (Fig. 2). Before drinking alcohol, IFC activity was higher in the right hemisphere than in the left hemisphere, but this difference was eliminated after drinking alcohol. These findings could not be attributed to the simple learning effect because drinking orange juice (placebo) did not affect hemispheric asymmetry in IFC activation (Fig. 3). Correlation analysis showed that subjects with right-lateralized IFC activity made fewer false-alarm responses in No-Go trials (Fig. 4), while subjects in whom alcohol reversed right hemispheric IFC superiority had higher false-alarm rates in No-Go trials (Fig. 5). Reaction times for Go trials did not significantly correlate with hemispheric asymmetry in IFC activation. In combination, these findings suggest that the right-lateralized IFC activity may mediate the acute effect of alcohol on response inhibition.

These findings are largely consistent with previous findings that the right IFC is critical for response inhibition (Aron et al. 2004; Bunge and Wright 2007). Functional neuroimaging studies have consistently indicated that the right IFC was activated in a wide variety of inhibitory control tasks that involved Go/No-Go tasks (Bunge et al. 2002; Chikazoe et al. 2007; Herrmann et al. 2005), stop signal tasks (Boecker et al. 2007; Rubia et al. 2003), and belief-bias reasoning tasks (Tsujii and Watanabe 2009, 2010; Tsujii et al. 2010a, b). The right IFC was also shown to be crucial in neuropsychological studies of patients with unilateral right prefrontal damage (Aron et al. 2003; Clark et al. 2007). These studies demonstrated that the extent of damage to the right IFC correlated significantly with the degree of impaired performance in response inhibition tasks. Further, other studies have suggested that the right IFC deficit may underlie the impaired response inhibition in patients with attention-deficit hyperactivity disorder (Durstun et al. 2006; Rubia et al. 1999, 2005, 2010).

This is the first study to demonstrate that right-lateralized IFC activation is critical for the alcohol-induced modulation of response inhibition. One previous functional magnetic resonance imaging (fMRI) has examined the neural correlates of the effect of alcohol on cognitive control processes using a Go/No-Go task (Anderson et al. 2011). However, that study addressed the error monitoring process with particular attention to the anterior cingulate cortex rather than addressing the response inhibition process in the lateral IFC region. Those investigators demonstrated that alcohol significantly reduced anterior cingulate cortex activity during false-alarm responses for No-Go trials (Anderson et al. 2011). Thus, this previous study does not contradict findings from the present study; rather, these

studies elucidate different aspects of the effect of alcohol on cognitive control processes.

#### Reduction of hemispheric asymmetry by alcohol

The present study showed that alcohol eliminated the RH superiority in IFC activity during inhibitory processes. In accordance with this finding, several neuroimaging studies previously reported that hemispheric asymmetry was reduced or eliminated by alcohol consumption (Soderlund et al. 2007; Wendt et al. 1994; Wendt and Risberg 2001). For example, Wendt et al. (1994) found that a visuo-spatial task activated the right-lateralized occipito-parietal cortex and that alcohol eliminated this hemispheric asymmetry. Other studies have shown that alcohol reduced left-lateralized prefrontal cortex activity during a verbal fluency task (Wendt and Risberg 2001).

Further, the present study showed that patients in whom right lateralization of IFC activity was disrupted by alcohol had higher false-alarm rates for No-Go trials, while subjects in whom alcohol did not reduce right lateralization could maintain low false-alarm rates (Fig. 5). Consistent with this finding, Wendt and Risberg (1994) found a significant positive correlation between scores on the visuo-spatial task and RH superiority in the occipito-parietal cortex. In their study, alcohol consumption disrupted the task performance, eliminating the RH superiority in the occipito-parietal cortex (Wendt et al. 1994). In addition, another study reported that left-lateralized IFC activity was reduced by alcohol only when the recognition memory performance was impaired (Soderlund et al. 2007). These findings suggest that alcohol produces a deleterious effect on cognitive performance via reduction of hemispheric asymmetry.

#### Limitations of this study

This study possesses several limitations. First, this study used a relatively low amount of alcohol (0.5 g/kg). By contrast,

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