Alcohol Consumption Impairs Detection of Performance Errors in Mediofrontal Cortex

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The anterior cingulate cortex (ACC) is a critical component of the human mediofrontal neural circuit that monitors ongoing processing in the cognitive system for signs of erroneous outcomes. Here, we show that the consumption of alcohol in moderate doses induces a significant deterioration of the ability to detect the activation of erroneous responses as reflected in the amplitude of brain electrical activity associated with the ACC. This impairment was accompanied by failures to instigate performance adjustments after these errors. These findings offer insights into how the effects of alcohol on mediofrontal brain function may result in compromised performance.

Alcohol consumption gives rise to a diffuse pattern of neurochemical changes (*1*) that lead to subtle impairments in cognitive operations (*2*). These effects modulate, for instance, the competence to drive a car (*3*, *4*). Adequate driving performance requires that cognitive operations can be adapted rapidly and flexibly in response to environmental cues (*5*). Behavioral adjustments may be prompted by external cues (e.g., traffic signs or a child suddenly crossing the street) or by the outcome of internal action monitoring. Adaptive control of behavior involves the ability to monitor ongoing processing in the cognitive system for signs of conflict or erroneous outcome (*6*). Psychophysiological and neuroimaging studies concluded that the anterior cingulate cortex (ACC) is a central component of the neural circuit for action monitoring (*7*, *8*). This control system (*9*–*12*) is involved in detecting the activation of erroneous or conflicting responses (*11*).

An important psychophysiological index of action monitoring is the error-related negativity (ERN) (*13*) or error negativity (*14*), an event-related brain potential (ERP) component most likely originating from the ACC (*10*–*12*, *15*). The recording of this component at the scalp reflects the detection of action errors and response conflicts (*6*, *16*). ERN is observed after errors of choice as well as failures to inhibit an action (*16*) and after action slips that are recognized as such by the subject as well as after errors that elude the subject's awareness (*17*). Thus, ERN reflects the activity of a preconscious action-monitoring system. The efficiency of other preconscious processes (such as the perceptual detection of acoustic deviance) is attenuated by alcohol (*18*). Here, we examine whether alcohol impairs the detection of action slips as expressed by ERN.

Subjects completed a version of the so-called "flanker task," chosen because of its demonstrated efficacy in eliciting ERNs after performance errors as induced by distractors (*11*, *15*, *16*). In the flanker task, a target arrow could be flanked by congruent or incongruent distractors (pointing in the same or opposite direction as the target, respectively); subjects were to respond to the direction of the target and to ignore distractor arrows. Subjects performed the task after a placebo and two different doses of alcohol that corresponded to blood alcohol concentrations of 0.0, 0.4, and 1.0 per mil (‰), respectively (*19*).

Adequate performance in the flanker task relies on effective engagement of interference control processes, such as response inhibition (*20*). If alcohol consumption were to induce a reduction in the efficiency of control processes in general, then impairments in both interference control and error detection could result. In that case, effects of alcohol on ERN amplitude would result indirectly from the more general effect, not from a direct effect on ACC. Although the proficiency of response inhibition can be reduced by alcohol consumption (*21*, *22*), this effect can be countered by strengthening motivation through instruction or reward (*23*). To prevent alcohol-induced changes in interference control from influencing the error monitoring results, subjects were instructed and trained to attain constant levels of flanker interference in reaction time (RT) across alcohol conditions. Likewise, instruction and practice kept response accuracy constant at a predesignated level to circumvent confounding effects of alcohol on the speed-accuracy tradeoff (*24*–*26*).

Processing speed was reduced by alcohol consumption [mean value M = 352, 360, and 382 ms in placebo, low-dose, and high-dose conditions, respectively; $F(2,26) = 7.51$; $P = 0.007$], whereas accuracy remained unaffected [$F(2,26) = 0.18$]. Helmert contrasts indicated that RT was shorter in placebo conditions than in the alcohol conditions [$F(1,13) = 11.18$, $P = 0.005$] and that RT was longer after the high-alcohol dose than after the low dose [$F(1,13) = 5.69$, $P = 0.033$]. This pattern of performance (detailed in table S1) justified an examination of the effects of alcohol on error monitoring and interference control without potentially confounding effects in terms of the speed-accuracy tradeoff or in terms of alcohol-induced stimulus misperception (which would also affect accuracy).

Compared to congruent trials, incongruent arrays were associated with slower responses [M = 348 versus 380 ms, $F(1,13) = 128.93$, $P < 0.001$] and more errors [M = 4.8 versus 19.8%, $F(1,13) = 125.94$, $P < 0.001$]. The magnitude of these typical congruity effects was not modulated by alcohol (table S1) [$F(2,26) = 0.08$ and 0.03 for RT and accuracy, respectively]. We further examined two measures of the inhibition of incorrect responses (*19*). First, the reduction of flanker interference effects that is typically observed in the RTs of slow, as compared to fast, responses provides a sensitive behavioral index of selective suppression of incorrect responses in conflict tasks (*20*, *27*). Alcohol failed to moderate this reduction of flanker interference (fig. S1) [$F(2,26) = 1.43$]. Second, the amplitude of the N2 component of the ERP provides an electrocortical expression of the engagement of response inhibition processes in conflict tasks (*28*) that is diminished by alcohol (*29*). The N2 is typically larger after incongruent as compared to congruent trials. Although this effect was replicated in the present data [$F(1,13) = 10.04$, $P = 0.007$], N2 amplitude was not modulated by alcohol [$F(2,26) = 2.24$]. Moreover, alcohol failed to influence the effect of congruence on N2 [$F(2,26) = 0.57$] (Fig. 1). Taken together, these results indicate that subjects successfully prevented the detrimental effects of incongruent distractors from being magnified by the effects of alcohol. Any effects of alcohol on error detection, which was examined next, are therefore not contaminated by effects on interference control. In addition to reflecting prefrontal response inhibition, N2 amplitude has recently been argued to represent contributions from ACC in monitoring conflicting activations during correct responses to incongruent stimuli (*15*). The absence of alcohol effects on N2, in that case, may suggest that the susceptibility of conflict monitoring in ACC to alcohol effects is prevented from being expressed in N2 ampli-

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tude, for instance because the relatively small effects on N2 are absorbed by noise or by simultaneous inhibition-related contributions to N2 (that are not modulated by alcohol in this study). We then turned to an analysis of a less equivocal index of error monitoring in ACC, the ERN.

Apparent in the ERPs associated with incorrect responses under placebo was a distinct ERN that was largest in amplitude at frontocentral scalp sites proximal to ACC and that attained its maximum amplitude shortly after response initiation (Fig. 2). The ERN was attenuated significantly by alcohol consumption [$F(2,26) = 6.61$, $P = 0.005$] (Fig. 3). Helmert contrasts confirmed that placebo conditions differed from the alcohol conditions [$F(1,13) = 13.32$, $P = 0.003$] whereas low- and high-dose conditions did not differ [$F(1,13) = 0.12$]. Like ERN, the effect of alcohol on ERN had a frontocentral scalp distribution (fig. S2). Thus, alcohol selectively affected the amplitude of ERN, an effect that was not confounded with alcohol-induced changes in accuracy levels or in the sensitivity to flanker interference.

If alcohol consumption impairs action monitoring in the brain, then some measurable and meaningful consequence of such failure should be evident. To the extent that the ACC fails to detect errors, it should fail also in signaling the need to instigate performance adjustments after these errors. Thus, under alcohol conditions subjects may fail to display the reduction in congruity effects typically observed after error commission (*27*, *30*). Indeed, although flanker interference effects were reduced after errors in placebo conditions [$F(1,13) = 5.01$, $P = 0.043$], no such reduction was observed in low- or high-dose alcohol conditions [$F(1,13) = 0.21$ and 0.40, respectively] (Fig. 4; details in table S2).

Although alcohol-induced detriments have been documented across a wide array of cognitive processes (*2–4*, *18*, *21–25*), the relation between effects on the brain and those on behavioral performance are still poorly understood (*1*). The present study documents that the consumption of alcohol (even in moderate doses) compromises performance by attenuating the brain's capacity to detect action slips. The ability to monitor ongoing processing in the cognitive system for signs of erroneous outcome is a prerequisite for adequate performance (involving flexible executive control to adapt cognitive operations in response to environmental prompts, such as when driving a car or when operating machinery). On the basis of the present data we cannot decide whether alcohol induces a pervasive reduction in action monitoring or rather an increase in the incidence of lapses in this ACC function. Both effects could potentially elicit the observed reduction in ERN amplitude.

Beyond the demonstration of ethanol-induced effects on ERP correlates of performance, the present ERP findings offer new empirical insights into how the effects of alcohol consumption on the mediofrontal brain may result in compromised performance. Even modest impairments in the detection of action slips by the ACC may result in deficits in signaling the need to instigate performance adjustments, as evidenced by adjustment failures in posterror performance.

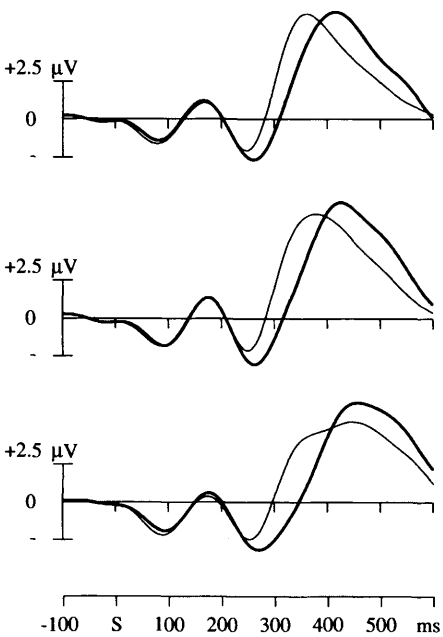


Fig. 1. Stimulus-locked grand-average ERPs recorded from the medial frontocentral electrode position FCz during correct responses to congruent (thin lines) and incongruent (thick lines) stimuli at placebo, low dose, and high dose (top, middle, and bottom, respectively). *S* denotes the time of the stimulus presentation. Relative to congruent trials, incongruent trials are characterized by an enhancement in the negative component identified as N2 (peaking between 200 and 300 ms poststimulus).

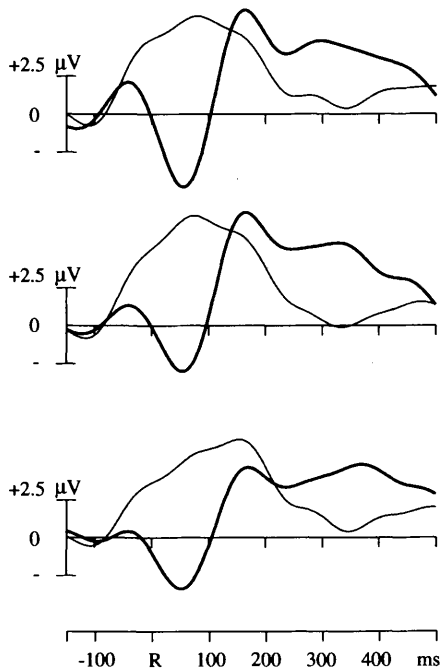


Fig. 2. Response-locked grand-average ERPs recorded from FCz during correct responses (thin lines) and during errors (thick lines), pooled across congruent and incongruent trials, at placebo, low dose, and high dose (top, middle, and bottom, respectively). *R* denotes the time of the response. Relative to correct responses, erroneous responses are characterized by a negative component identified as the ERN (peaking about 50 ms after the response). The ERN is followed by a positive deflection, typically identified as the error positivity (*16*).

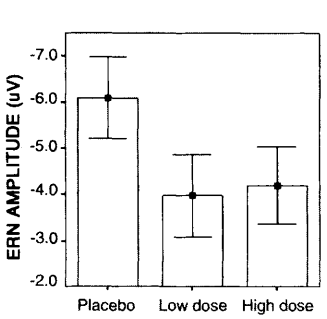
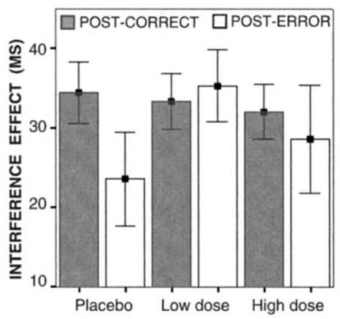


Fig. 3. (Left) Amplitude of the ERN component identified in the ERPs at FCz associated with incorrect responses under various doses of alcohol. Error bars reflect standard errors. ERN amplitude is reduced after alcohol consumption. **Fig. 4. (Right)** Performance adjustments after error commission. Interference effects on RT are reduced after errors (relative to the effects after correct responses) under placebo but not under alcohol conditions. Error bars as in Fig. 3.



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26. ERN amplitude increases when subjects favor accuracy over speed, whereas ERN amplitude is reduced as error rates increase (*13, 16*). If we would accept higher error rates after alcohol, then ERN amplitude might vary with alcohol dosage because of the effects of alcohol not on error detection (expressed in ERN amplitude) but on error rate (which in turn covaries with ERN amplitude). Should our procedure incur a speed-accuracy tradeoff to obtain comparable error percentages across alcohol conditions, then the relative emphasis on accuracy after alcohol should result in larger ERNs, which would oppose the alcohol-induced reduction in ERN amplitude anticipated here, thus rendering our approach a conservative one.
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Supporting Online Material
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Materials and Methods
Figs. S1 and S2
Tables S1 and S2

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Role of Melanopsin in Circadian Responses to Light

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Melanopsin has been proposed as an important photoreceptive molecule for the mammalian circadian system. Its importance in this role was tested in melanopsin knockout mice. These mice entrained to a light/dark cycle, phase-shifted after a light pulse, and increased circadian period when light intensity increased. Induction of the immediate-early gene c-*fos* was observed after a nighttime light pulse in both wild-type and knockout mice. However, the magnitude of these behavioral responses in knockout mice was 40% lower than in wild-type mice. Although melanopsin is not essential for the circadian clock to receive photic input, it contributes significantly to the magnitude of photic responses.

Several lines of evidence have recently indicated that melanopsin is a component of the photoreceptive system for circadian rhythms of mammals. Rods and cones are not necessary for circadian responses to light, which suggests that other photoreceptors exist (*1–3*). Melanopsin is found exclusively in the retina (*4–7*). Retinal ganglion cells of the inner retina that contain melanopsin mRNA and protein form dendritic plexuses in a network that allows these cells to capture photic stimuli across broad spatial domains (*7*). In these same cells, melanopsin is colocalized with pituitary adenylate cyclase activating polypeptide (PACAP); PACAP-containing ganglion cells form the retinohypothalamic tract that directly innervates the suprachiasmatic nucleus (SCN) (*8*), site of the mammalian circadian pacemaker. Furthermore, melanopsin-containing cells that innervate the SCN are intrinsically photosensitive in a manner consistent with their being irradiance detectors, but they are not suited for fine visual discrimination tasks (*5*). Cryptochrome photopigments are also found in the inner retina as well as in the SCN (*9, 10*), but there has been disagreement about their role in circadian photoreception (*9–12*).

Despite the data in support of melanopsin, there are no data to confirm a functional role in transducing photic input to the circadian pacemaker. Because input to the circadian pacemaker has several effects on the phase and period of circadian rhythms, one can test for melanopsin's involvement in these variables by investigating circadian photoresponsiveness in mice that lack melanopsin. We examined the capacity of mice with a targeted disruption of the melanopsin gene (fig. S1) to (i) entrain to a light/dark cycle, (ii) phase shift to brief light pulses, (iii) comply with Aschoff's rule [rhythm period (tau) increases with light intensity in nocturnal animals (*13, 14*)], and (iv) retain light-induced gene expression in the SCN (*15, 16*). We assessed circadian function in these mice by monitoring locomotor activity with infrared motion detectors (*17–19*). Melanopsin knockout (n = 7) and wild-type (n = 7) mice were housed with 12 hours of light per day for 13 to 16 days followed by constant darkness (DD). All animals were exposed to a 30-min bright-light pulse 16 days after DD began (*17, 18*). Mice remained in their home cages but were moved to a different room for the light pulse. The light pulse occurred four circadian hours [circadian time (CT) 16] after the onset of daily activity, at the time when light produces the maximal phase shift in most inbred mouse strains (*20, 21*). Because nonspecific factors associated with moving cages to novel locations sometimes produce phase shifts, all animals were given a control dark pulse 10 days after the light pulse at CT 16; animals were treated exactly as for the light pulse but remained in darkness during the procedure. Two weeks later, all mice were exposed to constant light (LL) for 14 days to test for conformity with Aschoff's rule. A separate group of wild-type (n = 3) and knockout (n = 3) mice was exposed to a 30-min light pulse, along with two mice exposed to a control dark pulse, on the second day of DD; c-*fos* expression was measured in the SCN of these animals by in situ hybridization (*17, 18*) as a cellular marker of SCN photosensitivity (*15, 16*).

The results of the three behavioral measures and the cellular index of circadian photoresponsiveness were consistent and show that melanopsin is not essential for transduction of photic stimuli to the circadian pacemaker. The light pulse at CT 16 produced robust phase delays in activity rhythms in both wild-type and knockout mice, although phase-shift magnitude was significantly lower (P = 0.02) in knockout mice than in wild-type mice (Fig. 1). Mean phase shifts for the dark pulse were <10 min for both groups. A second behavioral measure showed that diurnal rhythms under the LD cycle represent true entrainment rather than masking by the LD cycle because activity onsets in DD can

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