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Neurophysiological Pharmacodynamic Measures of Groups and Individuals Extended from Simple Cognitive Tasks to More “Lifelike” Activities

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Abstract

Objective—Extend a method to track neurophysiological pharmacodynamics during repetitive cognitive testing to a more complex “lifelike” task.

Methods—Alcohol was used as an exemplar psychoactive substance. An equation, derived in an exploratory analysis to detect alcohol’s EEGs effects during repetitive cognitive testing, was validated in a confirmatory study on a new group whose EEGs after alcohol and placebo were recorded during working memory testing and while operating an automobile driving simulator.

Results—The equation recognized alcohol by combining five times beta plus theta power. It worked well ($p < .0001$) when applied to both tasks in the confirmatory group. The maximum EEG effect occurred 2–2.5 hours after drinking (>1 hr after peak BAC) and remained at 90% at 3.5–4 hours (BAC $< 50\%$ of peak). Individuals varied in the magnitude and timing of the EEG effect.

Conclusion—The equation tracked the EEG response to alcohol in the confirmatory study during both repetitive cognitive testing and a more complex “lifelike” task. The EEG metric was more sensitive to alcohol than several autonomic physiological measures, task performance measures or self-reports.

Significance—Using EEG as a biomarker to track neurophysiological pharmacodynamics during complex “lifelike” activities may prove useful for assessing how drugs affect integrated brain functioning.

Keywords

EEG; pharmacodynamics; cognition; working memory; integrated brain function; lifelike task; automobile driving simulator; pattern recognition; alcohol; psychoactive drugs

Introduction

The aim of the current study was to track EEG changes for several hours following ingestion of a psychoactive substance during an exemplar “lifelike” activity by extending findings

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Conflict of Interest Statement

No industry support was received to perform the work described herein.

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made with well-controlled repetitive cognitive tasks as a reference. An exploratory study was first performed in which an EEG metric of the effect of a psychoactive substance was derived on a group of individuals while they performed simple repetitive cognitive tasks in the context of a placebo-controlled, cross-over design experiment. The validity of the metric was then assessed in a placebo-controlled cross-over confirmatory study by applying it to a new group of participants performing a repetitive working memory test and also while operating an automobile driving simulator over a four hour period. Alcohol was used as a model psychoactive substance because of its well established EEG effects (Begleiter and Platz, 1972; Cohen et al., 1993; Davis et al., 1941; Ehlers et al., 1989; Gevins and Smith, 1999; Ilan and Gevins, 2001; Lukas et al., 1986; Porjesz et al., 2005; Stenberg et al., 1994).

Beginning with Hans Berger (Berger, 1931; Gloor, 1969), EEG studies to detect or differentiate the effects of different classes or subclasses of psychoactive drugs or to examine dose-response relationships have traditionally been performed on subjects resting with their eyes closed (Fink, 1984; Hermann, 1982; Itil, 1974; Saletu et al., 1994; Galderisi and Sannita, 2006; Baskaran et al., 2012). Many evoked potential studies, most often employing variants of P300 oddball detection or N100 selective attention tasks, have examined psychoactive drug effects (Callaway and Halliday, 1982; Hammond et al., 1987; Dierks et al., 1994; Semlitsch et al., 1995; Curran, 1998; Hermens et al., 2005; Kenemans and Kahkonen, 2011; Musso et al., 2011; Diukova et al., 2012). Although guidelines for EEG studies of psychoactive drug effects during cognitive tasks have been published (Versavel et al., 1995), such studies are not widely performed (Gevins and Smith, 1999; Waters et al., 1998; Munoz-Torres et al., 2011). Such cognitive EEG testing is more sensitive and specific in detecting the neurological effect of psychoactive drugs than cognitive task performance measures themselves (Gevins et al., 2002; Ilan et al., 2004; Meador et al., 2007; Meador et al., 2010; Smith et al., 2006), with further improvement obtained by combining EEG and performance measures into single metrics (Gevins et al., 2002; Gevins et al., 2011b). However, in such studies, EEGs were recorded during highly simplified cognitive tasks that were repeated 50 or more times. Although such repetitive, stimulus-registered tests allow computation of both EEG and evoked potentials and provide useful information about the basic building blocks of neurocognitive processing, they obviously do not assess the integrated brain functioning of daily life. It is thus of interest to use EEG to assess pharmacodynamics during more complex tasks that were more like real world activities. While use of P300 as a “dual task” probe of subjects operating an automobile driving simulator has been reported (Wester et al., 2010), such “probe” measures are indirect and can be difficult to interpret. Directly measuring the effects of psychoactive substances on EEGs during complex lifelike or real world activities has rarely been undertaken (Ramaekers et al., 1992). Here we report initial progress in this regard by applying a metric of alcohol’s EEG effect during repetitive cognitive testing to a new group of intoxicated individuals operating an automobile driving simulator and also performing working memory tests. Analysis of a subset of this data has been used as part of a feasibility study of social brain function (Gevins et al., 2012b).

Methods

Participants

Exploratory Study—Participants were fifteen healthy adults (21–32 years, mean age 26 years, 8 females) recruited from the community who were all non-smokers and light to moderate users of alcohol (1 to 12 drinks per week). Participants with current or past neurological or psychiatric disorders or with recent or habitual use of illicit drugs or medications that may interact with alcohol were excluded.

Confirmatory Study—Participants were 15 healthy adults (21–58 years, mean age 31 years, 8 females) recruited from the community, none of whom participated in the Exploratory Study. These participants were licensed drivers and were light to moderate users of alcohol (1 to 10 drinks per week). Participants had the same health status and were subject to the same inclusion/exclusion criteria as in the Exploratory Study.

Both studies were reviewed and approved by a registered Institutional Review Board, and all participation was fully informed and voluntary.

BAC and Autonomic Physiological Measures

In the Exploratory Study, breath alcohol content (BAC) was measured 1, 2, 3 and 4 hrs post-ingestion. In the Confirmatory Study, BAC, blood pressure and heart rate were measured 1.5, 3 and 4.5 hrs post-ingestion.

Test administration

Exploratory Study—Participants performed a 2-back spatial working memory (WM) task in a block of 50 trials, lasting approximately 4 minutes, during which they had to decide whether the position of the current stimulus was in the same location as that of the stimulus presented two trials (~8 sec) previously (Gevins et al., 1990; Gevins and Smith, 2000; Gevins et al., 2011c; Gevins et al., 2012a). In this task, a stimulus (letter of the alphabet) was displayed for 200 ms in one of 12 positions on each trial, every 4.5 s. Participants had to decide whether the location of the stimulus on each trial matched the location of the stimulus presented two trials previously. Participants responded “match” or “no-match” on each trial with the left and right mouse buttons, respectively. Participants also performed an easier version of the WM task in which they had to decide whether the position of the current stimulus was the same as that of the first stimulus in the block of 50 trials. Stimulus and response parameters were identical to those of the 2-back task. Participants additionally performed a control task in which they were instructed to stare at a foveally presented dot and focus their attention on their breath for 1.5 minutes.

Confirmatory Study: Participants in this study performed simulated automobile driving followed by cognitive testing—The simulated driving task involved a 20-minute driving scenario using STISIM Drive (Systems Technology, Inc., Hawthorne, CA), a PC-based driving simulator. In STISIM, the participant operating the simulator sees a first-person view out of the windshield on a monitor display. The simulated automobile was controlled by a Microsoft SideWinder Force Feedback steering wheel and pedal set. The 20-minute scenario presented a variety of different conditions, ranging from long stretches of highway driving with few other cars to urban driving conditions with heavy traffic, stoplights, pedestrians, and other hazards typically encountered in everyday driving that require a high degree of control and rapid decision making. The top speed of the simulator was 80 mph and participants were instructed to reach the endpoint of the scenario as quickly as possible without causing accidents and following the rules of the road. For each test administration, participants performed one of 30 different scenarios, with the difficulty and number and timing of unpredictable events equated across scenarios. The simulation was displayed on a 20-inch LCD monitor and placed on a table at eye-level approximately two feet from the participant. The steering wheel was attached to the table, and the accelerator and brake pedals were placed on the floor with the position adjusted to suit each participant. A set of speakers was placed by the display monitor to produce background noise mimicking a car on the road such as wind gusts and car horns and to give turn instructions.

Following the driving simulator task, participants performed a 1-back working memory task, two standard neuropsychological tests without EEG recording (Backward Digit Span - BDS and Symbol Digit Modalities Test - SDMT), as well as several other cognitive tasks that are beyond the scope of this paper. In the WM task, participants had to decide whether the location of a dot stimulus on each trial was in the same of six possible locations as the dot on the immediately preceding trial (Gevins et al., 2011a). Stimulus duration and response requirements were the same as in the task used in the Exploratory Study. Trials lasted 4 sec and 50 trials were presented in a block lasting approximately 4 minutes.

Subjective Ratings

In the Confirmatory Study, following cognitive testing, participants completed a set of subjective rating scales. On a scale of 0 (“not at all”) to 1000 (“extremely”), participants were asked to rate how drunk, clumsy and impaired they felt and, if they had difficulty paying attention and remembering. Participants also completed the Karolinska Sleepiness Scale (KSS) to assess subjective sleepiness on a 9-point scale, ranging from 1 (very alert) to 9 (very sleepy).

EEG recording

Exploratory Study—EEGs were recorded from 40 electrodes, including the sites measured in the Confirmatory Study, using a stretchable cap with gel-filled electrodes. Signals were sampled at 256 Hz and band-pass filtered from 0.01 to 100 Hz. Prior to the analysis, sites were selected and the data was digitally filtered and down-sampled to match the data recorded in the Confirmatory Study.

Confirmatory Study—EEGs were recorded with a stretchable nylon cap with solid-hydrogel electrodes placed over bilateral and midline dorsolateral prefrontal locations (F3, F4, Fz), midline sensorimotor cortex (Cz), lateral superior parietal cortex (P3, P4), and midline parieto-occipital cortex (POz), referenced to digitally linked mastoids (Gevins et al., 2011a). These locations were selected, based on cognitive EEG studies with 40 or 100 electrodes (Gevins et al., 1996; Gevins et al., 1997), for their sensitivity to variations in cognitive task difficulty. Vertical and horizontal eye movements were monitored with electrodes placed above and lateral to each eye. Signals were sampled at 128 Hz and band-pass filtered from 0.1 to 35 Hz.

Procedures

Study design and dose were similar for the Exploratory and Confirmatory Studies. In each study, each participant completed alcohol and placebo test sessions occurring at least one week apart according to a double blind, randomized, counter-balanced design. In each session participants drank a glass of fruit juice that was either alcohol-laden or not. The alcoholic beverage contained 0.88g/kg of the participant’s body weight of 95% ethanol calculated to produce a peak BAC approaching 0.08 grams per 210 liters of breath (the legal limit for operating a motor vehicle in California). The placebo beverage had 5 ml of alcohol floated on top to mimic the smell and initial taste of the alcoholic beverage. In the Exploratory Study, participants were tested at 0.5, 1.5, 2.5 and 3.5 hrs post-ingestion, with each test interval lasting 0.5 hrs. In the Confirmatory Study, participants were tested at 0.5, 2 hrs and 3.5 hrs after drinking. Each test interval lasted 1 hr, with EEG recorded during the first 0.5 hr during simulated driving and working memory tasks. The first post-ingestion interval from each study most closely matches the time range of peak BAC (0.5 to 1.5 hrs) (Friel et al., 1999).

Data analysis

In the Exploratory Study data, the test interval with the largest EEG difference between alcohol and placebo was first identified, and then data from all tasks during that interval were used to compute an equation characterizing the EEG effect of alcohol. The data analysis in the Confirmatory Study was more extensive, including validation of the equation across three post-drinking intervals for both WM and driving tasks, relating results of the equation to a descriptive statistical EEG analysis, and relating results to BAC, task performance, autonomic and subjective measures.

Exploratory Study: EEG Spectral Analysis and Selection of Interval for Equation

Automatic detection and removal of artifacts due to eye movements and blinks, scalp muscle activity, head and body movements, and bad electrode contacts (Gevins et al., 1977; Gevins, 1984; Du et al., 1994) was followed by visual inspection of all decontaminated and raw data. For each of the four post-ingestion intervals, power spectral estimates were computed from Fast Fourier Transforms of the decontaminated, Hanning-windowed EEG data of each electrode of each participant by averaging the 50% overlapped 2-second periodograms over each task. The individual frequency component powers were averaged over the 2-back and easy WM tasks and the control task to derive a metric for assessing alcohol effects independent of the particular task, and the resultant values were then averaged into 3 standard bands, theta (4–7 Hz), alpha (8–13 Hz) and beta (13–18 Hz) determined in prior studies to be sensitive to alcohol's effect on the EEG (Begleiter and Platz, 1972; Lukas et al., 1986; Ehlers et al., 1989; Cohen et al., 1993; Gevins and Smith, 1999; Ilan and Gevins, 2001; Gevins et al., 2011b). The three banded powers and their standard deviations constituted a total set of six variables for each of the seven electrode sites. The power and standard deviation values were transformed to z-scores within subjects across alcohol and placebo conditions to reduce scale differences between the variables and between subjects (Gevins et al., 1979; Gevins, 1980; Gevins et al., 1987). The resulting values of the six variables at the seven electrode sites were then averaged over all sites to produce six final candidate variables characterizing alcohol's effect over the entire cerebral cortex for each of the post-ingestions intervals (Gevins et al., 2011b). Data from each interval were submitted to an ANOVA with condition and variable as within-subjects factors. Estimated effect size based on eta squared (η^2) was used to determine the interval with the largest difference between alcohol and placebo, and thus the time of maximum EEG effect, on which to derive an equation.

Exploratory Study: Use of Multivariate Divergence Analysis to Characterize the EEG Effects of Alcohol

The multivariate divergence analysis has been described in detail (Smith et al., 2001; Gevins et al., 2011b) and is briefly summarized here. Multivariate divergence analysis is a simple type of discriminant analysis used to find the subset of variables from a larger set of candidate variables that has the largest divergence between two conditions (Tou and Gonzalez, 1974). For each participant in the Exploratory Study, the values of the six candidate variables from the chosen interval for both alcohol and placebo sessions were submitted to the divergence analysis program which considered all possible subsets of up to three variables of the six and choose the subset that, considered together as a group, produced the highest divergence between the alcohol and placebo data sets and thus best recognized alcohol. In doing so, it did not necessarily choose subsets whose individual variables each had the most statistically significant differences between drug and placebo conditions if such variables were highly correlated with each other.

Confirmatory Study: BAC, Autonomic Physiological Measures and Subjective Ratings

The measures of heart rate, blood pressure, BAC and subjective ratings were submitted to univariate repeated measures ANOVAs to compare alcohol with placebo

conditions in the three post-ingestion intervals. Degrees of freedom in the ANOVAs were adjusted when appropriate using the Greenhouse-Geisser technique to correct for violations of the sphericity assumption.

Confirmatory Study: Task Performance—Driving performance was measured in terms of the number of off-road occurrences, the number of collisions with other vehicles, pedestrians, and road barriers, and the standard deviation of lateral lane position, as previous studies found that such measures are most sensitive to alcohol impaired driving (Arnedt et al., 2001; Marczyński et al., 2008). Performance accuracy (percent correct) and mean reaction time (milliseconds) were computed for the WM task. Scores from the BDS and SDMT neuropsychological tests were total number correct. Univariate repeated measures ANOVAs were performed to compare data from alcohol and placebo conditions in the three post-ingestion intervals to facilitate relating each of the measures with the EEG results. Degrees of freedom in the ANOVAs were adjusted when appropriate using the Greenhouse-Geisser technique to correct for violations of the sphericity assumption.

Confirmatory Study: Artifact Decontamination and EEG Spectral Analysis—

The same procedures as in the Exploratory Study were performed for each task and each interval to produce values for the six final candidate variables.

Confirmatory Study: Validation of the Equation Generated in the Exploratory Study—

The resulting subset of variables and their weightings was then tested on data from each of the three post-ingestion intervals of the Confirmatory Study to assess their reliability and generalizability to tracking alcohol effects in another subject group performing WM and simulated driving tasks. For each participant in the Confirmatory Study, for each task, for each condition (alcohol or placebo), and for each of the three intervals, the values of each of the variables chosen in the Exploratory Study were weighted by multiplying each by the percentage of the total divergence contributed by that variable in the Exploratory Study and dividing by its variance in the Exploratory Study. The resulting values were then summed with a constant to form a single score quantifying the neurophysiological effect of alcohol or placebo for that participant at that test interval. All scores were scaled such that the mean of scores from the Exploratory Study were -0.5 in the alcohol condition and +0.5 in the placebo condition. A relatively negative score in the alcohol condition indicated that the individual was affected by alcohol in a similar manner to that of participants in the Exploratory Study, while a relatively positive score in the alcohol condition indicated that the individual had variables values more typical of the placebo condition in the Exploratory Study.

For each task in the Confirmatory Study and for each of the intervals, data from each of the 15 participants were combined into scores for alcohol and for placebo conditions, using the up to three variables, weights, and variances calculated in the Exploratory Study. The participants' alcohol and placebo scores were then compared using a receiver-operator characteristic (ROC) analysis to quantify the recognition of alcohol and placebo (Hanley and McNeil, 1982; Gevins et al., 2011b). Participants' scores for each task from the alcohol and placebo conditions were used to generate a standard ROC curve to calculate area under the curve (AUC), sensitivity (correctly identifying the alcohol condition), and specificity (correctly identifying the placebo condition) values for each test interval. AUC was then used as a metric of the alcohol effect, and its significance was calculated using the normal distribution from the z ratio computed as the AUC minus 0.5 divided by the standard error for AUC = 0.5, the null hypothesis. Differences between two AUCs were assessed with a two-sample z-test.

Confirmatory Study: Descriptive Statistics and Comparisons of Measures—To compare the results of the divergence analysis in the Confirmatory Study with results of a

descriptive statistical analysis, univariate ANOVAs with repeated measures over intervals were used to compare data from alcohol and placebo conditions across the three post-ingestion intervals for the theta, alpha and beta EEG variables. Degrees of freedom in the ANOVAs were adjusted when appropriate using the Greenhouse-Geisser technique to correct for violations of the sphericity assumption. Pearson correlations were computed to assess the correlation of the EEG scores with BAC, task performance scores, physiological measures and subjective ratings, as well as to determine the relations between the various non-EEG measures.

Results

Exploratory Study: Interval with Largest EEG Effect, BAC, WM Performance and Equation to Recognize Alcohol

The second test interval 1.5 to 2 hrs post ingestion had the largest EEG difference between alcohol and placebo ($F(1,14)=48.22$, $p<.0001$, $\eta^2=0.62$). BAC was .06 (s.d. .01) for this interval. (The peak value of BAC, .07 was reached during the prior interval an hour earlier.) There were no alcohol-related changes in either accuracy or reaction time of the difficult WM task (accuracy $t(1,14)=.54$, $p>.05$; reaction time $t(1,14)=1.84$, $p>.05$). In the easy WM task, accuracy but not reaction time was adversely affected by alcohol during this interval (accuracy $t(1,14)=2.17$, $p<.05$; reaction time $t(1,14)=.52$, $p>.05$). Figure 1a shows EEG power spectra of the six candidate variables for alcohol and placebo conditions during this interval and Figure 2 shows the z-transformed values of the six variables submitted to the divergence analysis. The divergence analysis selected a combination of two measures to discriminate alcohol from placebo: increased beta band power (weight 0.59) and increased theta band power (weight 0.12). The equation was as follows: If $(-.59 * \text{beta}) + (-.12 * \text{theta}) + 0.71 < .19$, then the segment was classified as being from the alcohol data sample. This resulted in an Area Under the Curve (AUC) of 0.98 ($z(29)=4.5$, $p<.0001$), with 100% sensitivity and 93% specificity in recognizing alcohol and placebo.

Confirmatory Study

BAC, Physiological Measures and Subjective Ratings (Table 1). BAC's were .07, .05 and .03 for post-ingestion intervals 1, 2 and 3, respectively ($p<.0001$). There was a significant condition x interval interaction for BAC ($p<.0001$), with BAC decreasing across intervals in the alcohol condition. Heart rate increased ($p<.01$) following alcohol ingestion, but blood pressure did not differ from placebo. Alcohol also produced significant increases in self reports of drunkenness, clumsiness, and difficulty remembering (all p 's $<.01$), but did not affect subjective assessments of drowsiness. The condition x interval interactions were significant for self reports of drunkenness ($p<.0001$), clumsiness ($p<.0001$) and difficulty remembering ($p<.01$), with drunkenness and clumsiness decreasing across the three intervals after drinking alcoholic beverages, and reports of difficulty remembering decreasing from the second to the third interval.

Neuropsych Tests (Table 1)—Alcohol did not affect performance on either Backwards Digit Span or the Symbol Digit Modalities Test.

WM task (Table 1)—There were no significant changes in accuracy or reaction time consequent to alcohol.

Simulated Driving (Table 1)—There were no significant effects of alcohol on any of the three driving performance measures. There was, however, a significant condition (alcohol vs. placebo) by interval interaction for the number of occurrences of driving off road ($p<.05$), with alcohol increasing the number of off road occurrences in the first post-ingestion

interval. There was also a significant condition by interval interaction for the number of collisions ($p < .05$), although none of the post-hoc comparisons of alcohol versus placebo for any of the three intervals was significant.

Application of Exploratory Equation to Confirmatory Study Data—The equation performed well when applied to the Confirmatory Study (Table 2), with good discrimination of alcohol and placebo across all three post-ingestion intervals and both tasks (AUC 0.91; 83% sensitivity, 86% specificity; $p < .0001$). EEG scores following alcohol ingestion were lower than placebo at each of the intervals ($t > 2.5$, $p < .05$ in all cases) for both tasks, averaging -0.34 for alcohol and $+0.38$ for placebo across intervals and tasks. AUC for the WM task increased from .80 ($p < .01$) during the first interval to 1.00 ($p < .0001$) during the second, and then fell to .90 ($p < .001$) during the third. AUC during the first interval was lower than the second interval ($p < .05$), but the decrease from the second to the third interval was not significant. AUCs for driving remained constant across the three intervals (.90, .90 and .88, respectively; all p 's $< .001$).

Descriptive Statistics—EEG power spectra for the WM task during interval 2 are shown in Figure 1b and for the simulated driving task in Figure 1c. Z-score values for the six candidate EEG variables for alcohol and placebo conditions in each of the three post-drinking intervals are shown for the WM task in Figure 3a and for the simulated driving task in Figure 3b. Alcohol increased alpha and beta band power and standard deviation for both WM (alpha power $F(1,14)=68.75$, $p < .0001$; alpha SD $F(1,14)=66.92$, $p < .0001$; beta power $F(1,14)=105.92$, $p < .0001$; beta SD $F(1,14)=92.76$, $p < .0001$) and driving tasks (alpha power $F(1,14)=12.46$, $p < .01$; alpha SD $F(1,14)=26.89$, $p < .0001$; beta power $F(1,14)=29.47$, $p < .0001$; beta SD $F(1,14)=28.98$, $p < .0001$), and increased theta band power and standard deviation for the WM task (theta power $F(1,14)=9.13$, $p < .01$; theta SD $F(1,14)=9.53$, $p < .01$). For the WM task, there were significant condition by interval interactions for beta power ($F(2,28)=3.69$, $p < .05$) and theta power ($F(2,28)=4.17$, $p < .05$), with more beta power in the alcohol condition at each interval and theta power increasing from the first to second interval in the alcohol condition. There were also significant condition by interval interactions for WM beta SD ($F(2,28)=4.29$, $p < .05$) and WM theta SD ($F(2,28)=4.55$, $p < .05$), with beta and theta power standard deviations increasing from the first to second interval in the alcohol condition. For WM and driving tasks, there was no condition by interval interaction for alpha (WM $F(2,28)=2.02$, $p > .05$; driving $F(2,28)=2.29$, $p > .05$) or for driving beta power ($F(2,28)=.04$, $p > .05$), as they remained elevated in all three post-ingestion intervals in both conditions. There was a significant condition by interval interaction for theta power during driving ($F(2,28)=5.83$, $p < .01$), attributable to an increase in the alcohol condition from the first to second interval.

Timing and Relationship of Alcohol Effects on BAC, Task Performance, Subjective Self-Assessments and EEG—BAC peaked at .07 in the first interval and steadily declined to .03 by the third interval, as did self-assessments of drunkenness and clumsiness. The self-assessment of difficulty remembering and paying attention was elevated in the first and second intervals and declined in the third. The only clear sign of an alcohol-related performance decrement (increased number of driving off road incidents) occurred in the first interval. EEG AUCs indicated a large alcohol effect for both WM and driving tasks in all three intervals, the only difference being that the WM task reached the maximum possible value of 1.0 in the second interval while the value of ~ 0.9 did not change for driving (Figure 4).

EEG alcohol scores were inversely related to BAC during both WM and driving tasks (WM $r = -.604$, $p < .01$; driving $r = -.463$, $p < .01$). They were unrelated to task performance measures (all p 's $> .05$), but were inversely related to participants' self-reports of increasing

drunkenness (WM $r = -.412$, $p < .01$; driving $r = -.378$, $p < .01$) and difficulty remembering (WM $r = -.390$, $p < .01$; driving $r = -.348$, $p < .01$). BAC was not related to WM accuracy ($r = -.220$, $p > .05$) but was related to number of off-road driving incidents ($r = .385$, $p < .01$). Heart rate increased with increasing BAC ($r = .410$, $p < .01$). EEG scores also decreased with increasing heart rate (WM $r = -.348$, $p < .01$; driving $r = -.309$, $p < .05$) due to the predominant alcohol effect.

Individual Differences In Neurophysiological Pharmacodynamics (Figure 5)—

The BAC of 14 of the 15 participants was maximal in the first interval and decreased across the second and third intervals, the exception being participant u29 who's BAC peaked in the second interval at the highest value recorded in the study. Although the EEG alcohol scores over the four-hour post-drinking period showed considerable individual variation in both magnitude and timing, scores for 14 of the 15 individuals were negative at some point following drinking in both WM and driving tasks. With few exceptions (u01 and u32), the EEG alcohol effect persisted over the four hour period irrespective of whether BAC fell off slowly (u02, u18, u29) or more rapidly (u20, u22, u27, u30 and u31). Participants who differed the most from the group tended to show no EEG or performance response to alcohol or a delayed EEG response accompanied by poor performance. For instance, while u01's driving EEG alcohol scores were positive (like the placebo condition) during all three intervals and her driving performance was not affected by alcohol, her WM EEG scores were decremented in the two post-ingestion intervals where her WM performance was below chance. Similarly, u07 and u26 had minimal or no WM or driving EEG response to alcohol in the first interval but showed a stronger response decrement than the group in the second interval corresponding with markedly poor task performance. While over the group the relationship between EEG alcohol scores and task performance was not significant, there were a number of individuals for whom extremes of performance were accompanied by EEG scores that differed markedly from the group. Three (u07, u26, u31) of the five (u01, u07, u22, u26, u31) participants with the worst alcohol-related decrements in WM performance, had WM EEG alcohol scores that far exceeded the group value and which occurred in the same interval as the worst performance. Three (u26, u29, u30) of the four participants (u23, u26, u29, u30) with the worst driving performance (two or more off road incidents in one interval) had maximal driving EEG alcohol scores that were also well beyond the group average but only in one (u30) did that occur during the interval with the worst performance. The two participants (u01 and u32) with no off road incidents had driving EEG alcohol scores reflecting a much smaller effect than the group.

Discussion

In the current study an equation, developed in an exploratory analysis to detect the effect of a psychoactive substance on EEGs during repetitive cognitive testing, was applied to a new group of participants performing a working memory task and a more complex and "lifelike" activity after ingesting the same psychoactive substance. Operating an automobile driving simulator was used as an exemplar "lifelike" activity, and alcohol was used as an exemplar psychoactive substance because of its well documented EEG effects. The equation, which quantified alcohol's characteristic broad spectrum increase in EEG power by summing five times the amount of EEG beta plus theta band power, worked well in tracking the cognitive neurophysiological effect of alcohol over a four hour period in the new group of participants. The EEG metric was more sensitive to alcohol and more correlated with BAC than several autonomic physiological measures, several standard neuropsychological and cognitive tests, operating an automobile driving simulator and several self-report measures. The maximum EEG effect occurred 2 to 2.5 hours post-ingestion which was more than an hour after BAC was maximal. The EEG effect remained at 90% of its maximum level 3.5 to 4 hours following ingestion, while the BAC fell to less than half its peak value, consistent

with prior observations that the CNS effect of alcohol persists well beyond its initial metabolic absorption (Martin et al., 1984; Ilan and Gevins, 2001). In the Exploratory Study and in the Confirmatory Study, the tasks performed were the same in both alcohol and placebo conditions, and there were minimal differences in motor performance variables between conditions in both studies. Therefore, it seems most likely that the equation actually characterized the EEG effect of alcohol rather than uncontrolled factors in the experiment such as possible differences between alcohol and placebo in the amount of motor activity (Gevins et al, 1979).

The dose of alcohol administered increased heart rate and was adequately calibrated so that 14 of the 15 participants reached BACs within $\pm .02$ of the target level of .08, the California legal limit for driving. Although a double-blind, placebo-controlled cross-over design was used, participants were well aware of being inebriated, and reported having impaired coordination and cognition, with maxima in subjective scale effects coincident with maximum BAC. By contrast, alcohol did not affect performance on two standard clinical neuropsychological tests (backwards digit span and symbol digits modalities test) or on an n-back working memory task widely used in neuroimaging studies. It also did not affect overall automobile driving simulator performance, although the number of off-road occurrences did increase 30–50 minutes after ingestion, coincident with maximal BAC. In prior studies showing adverse cognitive effects of alcohol (e.g. longer reaction times and decreased accuracy in simple vigilance and sustained attention tasks (Koelega, 1995; Rohrbaugh et al., 1988) and modified response biases in immediate memory and continuous performance tasks (Dougherty et al., 2000)), such effects were most reliably observed at dose levels ~20% higher than those used in the current study.

With few exceptions (e.g. P300 used as a probe in Wester et al., 2010), prior research on alcohol and driving has not focused on direct neurophysiological measures of alcohol's impact on brain function. Alpha, beta and to a lesser extent theta band EEG power and standard deviation were increased by alcohol, consistent with prior studies (Begleiter and Platz, 1972; Cohen et al., 1993; Ehlers et al., 1989; Gevins and Smith, 1999; Ilan and Gevins, 2001; Lukas et al., 1986; Stenberg et al., 1994; Gevins et al., 2002). Driving and WM task alpha and beta power were greater in all three intervals compared to placebo, while theta power increased from the first to second interval. The latter may reflect the time required for alcohol to affect mass neural synchronization to the point sufficient to involve sufficient populations to increase theta power (Freeman, 1975).

Individual differences in EEG response to alcohol were assessed by applying the equation to the data of each of the participants (Gevins et al., 2011b). The EEG effect of alcohol generally persisted over the four hour period irrespective of whether BAC fell off slowly or more rapidly. Although the pattern of change in the EEG alcohol scores over the four hour period showed considerable individual variation in both the magnitude and particularly the timing of the maximum response to alcohol, EEG alcohol scores for 14 of 15 individuals were predominantly negative in both WM and driving tasks. While overall there was little relationship between EEG alcohol scores and performance, there were a number of cases where extremes of performance were accompanied by EEG scores that differed markedly from the group pattern. Individuals with a delayed EEG effect tended to have poor task performance when the EEG effect became manifest. Individuals with the worst WM and driving performance had corresponding EEG scores well below the group average, while the two best drivers had driving EEG scores that were markedly less affected by alcohol than the group. Because of the small number of participants, tantalizing observations such as these can only be taken as suggestive of hypotheses for future research.

The results reported here are merely a first step that is illustrative of how EEG measures can be applied to track changes over hours in the cognitive pharmacodynamics of a psychoactive substance during complex “lifelike” activities, and we do not wish to attach too much significance to the specific findings. Consistent with the purpose of demonstrating the use of the EEG as a biomarker in this context, a global effect on the cerebral cortex was obtained by averaging the data from the individual electrodes. Regional cortical effects of alcohol were not examined as could have been done by fitting an equation to each electrode separately (Gevins, et al., 1979; Gevins, 1980) or by application of principal components analysis (John et al., 1977), statistical pattern recognition methods (Gevins et al., 1983; Gevins et al., 1987), global field power (Lehmann, 1987; Lehmann, 1988), independent components analysis (Makeig et al., 1996), etc. Future studies with larger subject populations might fruitfully explore differential effects on frontal, parietal and other cortical areas, for instance using high resolution EEG methods with many electrodes, spatial deblurring and MRI co-registration (Gevins et al., 1995; Gevins et al., 1999). Amongst the many types of analysis available, the simplest form of spectral analysis into traditional frequency bands was used to parameterize the EEG. The beta band and theta band EEG power variables chosen by the divergence analysis may not be the best measures of alcohol’s effect. They are merely spectral analysis variables that were most effective in combination when characterizing alcohol effects during performance of repetitive cognitive tasks in one sample of healthy adults. Other analyses such as, time-frequency analysis, independent component analysis, autoregressive models of various sorts, nonlinear dynamical models, etc. might be more effective. The specific EEG measures and their weighting chosen by whatever type of analysis was used to recognize alcohol would likely vary somewhat if a different group of participants, performing the same or different tasks, were used in the exploratory analysis, and the combination of variables chosen would be different for other drugs. Other limitations of the current study include: 1) Since it is focused on extending EEG measures of psychoactive substance effects during performance of simple repetitive cognitive tasks to more complex and “lifelike” tasks, EEG during resting is not compared with EEG during task performance; 2) Information about whether relatives of participants were alcoholics was not obtained and the results therefore do not address this issue (Porjesz et al., 2005); 3) Alcohol dose for each participant was based on body weight rather than body mass index and possible differences in EEG results between the two cannot be addressed.

The results suggest that EEG during both repetitive cognitive testing and more complex “lifelike” activities may be helpful in tracking group and individual neurophysiological pharmacodynamics and effects of psychoactive substances on basic cognitive processes and integrated brain functioning, in relation to other biomarkers and behavior. Future research can further develop this approach by application to other drugs, tasks and populations, using EEG metrics by themselves or in combination with behavioral performance measures during complex “lifelike” activities. It may also be possible to make such EEG biomarker measurements simultaneously on groups of people to assess the effects of psychoactive substances on social brain function (Gevins et al., 2012b).

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Highlights

- In an exploratory-confirmatory paradigm, an equation combining beta and theta EEG power tracked the effect of an exemplar psychoactive substance (alcohol) for four hours.
- The equation, derived on repetitive cognitive task EEG data in the Exploratory Study, worked well when applied in the Confirmatory Study to track alcohol's EEG effects on a working memory task and on a simulated automobile driving task.
- This suggests that EEG biomarkers may prove useful for assessing, both in groups and individuals, neurophysiological effects of psychoactive substances on both basic cognitive processes and integrated brain functioning in relation to other biomarkers and behavior.

Figure 1.

EEG power spectra for alcohol (dark solid line) and placebo (light dashed line) data for: a) the cognitive tasks 1.5 to 2 hrs after drinking in the Exploratory Study, b) the working memory task 2 to 2.5 hrs after drinking in the Confirmatory Study, and c) the simulated driving task 2 to 2.5 hrs after drinking in the Confirmatory Study. Alcohol increased power across a broad swath of the spectrum.

Figure 2.

Values for the six candidate EEG variables for alcohol and placebo conditions 1.5 to 2 hrs after drinking in the Exploratory Study. Bars show means over participants of EEG power and within-participant standard deviation of power in z-units in theta, alpha and beta bands. Error bars are standard deviation. The divergence analysis selected the combination of five times beta plus theta band power to form a simple equation that recognized alcohol's EEG effect. That equation was then applied to a new group of participants in the Confirmatory Study.

Figure 3.

Confirmatory Study values for the six candidate EEG variables for alcohol and placebo conditions in each of the three post-drinking intervals. Bars show means over participants of EEG power and within-participant standard deviation of power in z-units in theta, alpha and beta bands during the Working Memory (a) and Simulated Driving (b) tasks. Alcohol increased alpha and beta band power and standard deviation for both WM and driving tasks, and increased theta band power and standard deviation for the WM task. WM and Driving task alpha and beta power were greater in all three intervals compared to placebo, while theta power increased from the first to second interval. Error bars are standard deviation.

Figure 4.

Breath Alcohol Content (times ten) and EEG Area Under the Curve alcohol effect values during Working Memory and Driving tasks for the Confirmatory Study group during the three post-drinking intervals. BAC was maximal in Interval 1, 0.5 to 1 hour after drinking, while the maximum EEG effect occurred more than an hour later in Interval 2. The EEG effect remained at 90% of its maximum level in Interval 3, 3.5 to 4 hours following ingestion, while the BAC fell to less than half its peak value.

Figure 5.

Breath Alcohol Content values (times ten), and alcohol EEG scores (sign inverted) for Working Memory and Driving tasks for the three post-drinking intervals for the group (left-most set of data) and for each of the fifteen participants in The Confirmatory Study. The EEG scores were computed by applying the equation from the Exploratory Study to each participant's alcohol condition data. An ! over a bar indicates that the sign of the EEG score was not inverted and that the effect of alcohol was more like placebo. Although the EEG alcohol scores over the four-hour post-drinking period showed considerable individual variation in both magnitude and timing, scores for 14 of the 15 individuals were negative in both WM and driving tasks at some point following drinking alcohol.

Table 1

Validation Study physiological, neuropsychological test and task performance, and subjective self-rating measure means (and standard deviations) for alcohol and placebo conditions for the three post-ingestion intervals. Driving and working memory tasks were performed during the first half hour of each interval while the other measures were taken during the last half hour.

	Interval 1 .5 to 1.5 hrs		Interval 2 2 to 3 hrs		Interval 3 3.5 to 4.5 hrs		Anova and Significance
	Alcohol	Placebo	Alcohol	Placebo	Alcohol	Placebo	
Physiological							
BAC	.07 (.01)	.00 (.00)	.05 (.02)	.00 (.00)	.03 (.02)	.00 (.00)	F(1,14)=165 ****++
BP	120/76 (13/10)	120/76 (15/12)	123/74 (18/11)	118/80 (20/14)	128/79 (20/12)	123/81 (17/12)	F's(1,14)<3.05 ns
HR	86 (12)	78 (13)	83 (8)	74 (11)	83 (8)	73 (9)	F(1,14)=9.61 *
Neuropsych Tests & Tasks							
BDS	9(3)	9 (2)	9 (2)	9 (3)	10 (2)	10 (2)	F(1,14)=.58, ns
SDMT	51 (10)	55 (12)	53 (10)	57 (12)	56 (13)	58 (12)	F(1,14)=4.46, ns
WM % correct	80 (18)	82 (24)	82 (18)	83 (24)	86 (11)	89 (12)	F(1,14)=.13 ns
WM RT (ms)	739 (146)	756 (136)	727 (154)	739 (178)	714 (154)	712 (154)	F(1,14)=.18 ns
DR lane position (sd feet)	10 (3)	10 (2)	11 (2)	12 (3)	12 (2)	11 (3)	F(1,14)=.15 ns
DR # off road occurrences	1 (.8)	.3 (.8)	.4 (.6)	.4 (.6)	.1 (.4)	.4 (.6)	F(1,14)=1.22 ns ⁺
DR # collisions	8 (4)	5 (3)	6 (2)	8 (4)	7 (4)	5 (3)	F(1,14)=2.41 ns ⁺
Subjective Scales (0–1000)							
Drowsy	6 (2)	5 (2)	5 (2)	4 (2)	4 (2)	3 (2)	F(1,14)=1.46, ns
Drunk	629 (260)	5 (11)	333 (290)	7 (26)	81 (131)	0 (1)	F(1,14)=48.49 ****++
Clumsy	505 (309)	83 (107)	249 (321)	37 (83)	124 (221)	30 (77)	F(1,14)=17.32 ****++
Difficulty Remembering	690 (175)	354 (276)	571 (251)	305 (244)	258 (237)	341 (277)	F(1,14)=12.67 ****++

BAC = breath alcohol content; BP = blood pressure (systolic/diastolic mmHg); HR = heart rate (beats per minute); BDS = backward digit span; SDMT = symbol digit modalities test; WM = working memory task; DR = simulated driving task; RT = reaction time; ms = milliseconds; Drowsy = Karolinska Sleepiness Scale. ns = not significant;

* p<.01,

** p<.001,

*** p<.0001;

Results of applying the Exploratory Study equation to the Confirmatory Study data. Each entry shows mean (standard deviation) of alcohol and placebo EEG divergence scores, the Area Under the Curve (AUC) and its 95% confidence interval for recognizing alcohol from placebo and its significance, the sensitivity of recognizing alcohol and the specificity of recognizing placebo.

Table 2

	Working Memory		Driving	Across Tasks	
Interval 1	EEG Score Alcohol	-0.23 (0.39)	-0.19 (0.29)	-0.21 (0.34)	
0.5 to 1 hrs	EEG Score Placebo	0.34 (0.54)	0.35 (0.29)	0.35 (0.43)	
	AUC (95% CI)	0.80[*] (0.63–0.96)	0.90^{**} (0.79–1.01)	0.85^{***} (0.75–0.95)	
	Sensitivity (%)	73	80	77	
	Specificity (%)	73	87	80	
Interval 2	EEG Score Alcohol	-0.53 (0.30)	-0.32 (0.46)	-0.43 (0.39)	
2 to 2.5 hrs	EEG Score Placebo	0.59 (0.35)	0.37 (0.32)	0.48 (0.35)	
	AUC (95% CI)	1.00^{***} (1.00–1.00)	0.90^{**} (0.77–1.04)	0.95^{***} (0.89–1.02)	
	Sensitivity (%)	93	80	87	
	Specificity (%)	100	93	97	
Interval 3	EEG Score Alcohol	-0.37 (0.31)	-0.41 (0.33)	-0.39 (0.32)	
3.5 to 4 hrs	EEG Score Placebo	0.32 (0.39)	0.28 (0.50)	0.30 (0.44)	
	AUC (95% CI)	0.90^{**} (0.79–1.01)	0.88^{**} (0.74–1.02)	0.90^{***} (0.81–0.98)	
	Sensitivity (%)	87	87	87	
	Specificity (%)	80	80	80	
Across Intervals	EEG Score Alcohol	-0.38 (0.35)	-0.31 (0.37)	-0.34 (0.36)	
	EEG Score Placebo	0.42 (0.44)	0.33 (0.38)	0.38 (0.41)	
	AUC (95% CI)	0.92^{***} (0.86 – 0.98)	0.90^{***} (0.83–0.97)	0.91^{***} (0.86–0.95)	
	Sensitivity (%)	84	82	83	
	Specificity (%)	84	87	86	

* p<0.01,

** p<0.001,

*** p<0.0001.