The effect of acute alcohol on motor-related EEG asymmetries during preparation of approach or avoid alcohol responses

Korucuoglu, O.; Gladwin, T.E.; Wiers, R.W.

DOI
10.1016/j.biopsycho.2015.12.012

Publication date
2016

Document Version
Final published version

Published in
Biological Psychology

License
Article 25fa Dutch Copyright Act (https://www.openaccess.nl/en/in-the-netherlands/you-share-we-take-care)

Link to publication

Citation for published version (APA):
The effect of acute alcohol on motor-related EEG asymmetries during preparation of approach or avoid alcohol responses

Ozlem Korucuoglu a,b,*1, Thomas E. Gladwin a,c, Reinout W. Wiers a

a Addiction, Development and Psychopathology (ADAPT)-lab, Department of Psychology, University of Amsterdam, Weesperplein 4, 1018 XA Amsterdam, The Netherlands
b Department of Psychological Sciences, University of Missouri, Columbia, USA
c Research Centre—Military Mental Health, Ministry of Defense, The Netherlands

ARTICLE INFO

Article history:
Received 29 March 2015
Received in revised form
15 November 2015
Accepted 21 December 2015
Available online 4 January 2016

Keywords:
Alcohol approach bias
Alpha
Beta
Asymmetry
Acute alcohol
Prospective predictions

ABSTRACT

Alcohol approach tendencies have been associated with heavy drinking and play a role in the transition to alcohol abuse. Such cognitive biases might predict future alcohol use better under a low dose of alcohol. The aim of this prospective study was to investigate both the magnitude and the predictive power of alcohol-induced changes on approach–avoidance bias and bias-related cortical asymmetries during preparation response across heavy and light drinking adolescents. In heavy drinking adolescents greater approach-related asymmetry index in the beta-band was observed for soft-drink cues compared to alcohol ones and this increase was associated with increase in difficulty to regulate alcohol intake. Earlier findings demonstrated that young heavy drinkers hold both positive and negative implicit alcohol associations, reflecting an ambiguity towards alcohol. The increase in approach related beta-lateralization for soft-drink cues measured in this study may represent a compensatory effort for the weaker S–R mapping (approaching soft drink). The MRAA findings in this study may highlight a mechanism related to overcompensation due to ambivalent attitudes towards drinking in our heavy drinking sample who had greater problems to limit their alcohol intake compared to light drinkers. Moreover, a relatively strong approach soft-drink and weak approach alcohol reaction-time bias after alcohol predicted decreasing drinking; suggesting that the capacity to control the bias under alcohol could be a protective factor.

Published by Elsevier B.V.

1. Introduction

In recent years, researchers have shown an increasing interest in drug-related cognitive biases due to their value in predicting drug-related behaviours and clinical outcomes. Cognitive biases have been found in adolescents and young adults in attentional processes (e.g. Field, Christiansen, Cole, & Goudie, 2007), action tendencies (approach biases, Field, Kieman, Eastwood, & Child, 2008; Wiers, Rinck, Dictus, & van den Wildenberg, 2009) and implicit memory associations (e.g. Thush et al., 2007). In adolescents these biases have been found to be predictive of drinking (memory bias: Thush & Wiers, 2007; Thush et al., 2008; approach bias: Peeters et al., 2013). Note that some of these studies involved high-risk groups, either defined by education (special education for adolescents with externalizing problems, Peeters et al., 2013) or by genotype (e.g., Wiers et al., 2009). Training varieties of these tasks have been found to change the bias and reduce relapse rates (Eberl et al., 2013; Schoenmakers & Wiers, 2010; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). Such results have clinical implications but are also of theoretical interest. Studies in young samples may provide important insights for our understanding of the role of automatic motivational processes in the continuation of drug use later in life (i.e. Curtin, Barnett, Colby, Rohsenow, & Monti, 2005).

The approach avoidance task (AAT) assesses automatically activated action tendencies to approach or avoid a category of stimuli (Rinck & Becker, 2007; Wiers et al., 2009). Facilitations in response times when approaching alcohol-related stimuli compared to avoidance response indicates that alcohol stimuli are compatible with approach versus avoidance responses. These stimulus-response compatibility effects are thought to emerge when implicit action tendencies are in line with the instructed responses during congruent blocks and/or it is difficult to maintain a stimulus-response association during incongruent blocks. If indeed the motivational value of the alcohol cues drives the bias in the alcohol AAT, facilitation in approach alcohol responses might...
be related to subjects’ drinking profile. This was exemplified by the finding of a stronger approach bias in heavier drinkers (Field et al., 2008; especially in those with a g-allele in the OPRM1 gene, Wiers et al., 2009).

Stimulus-response compatibility effects on motor programs can be studied through the hand-related response preparation. Regarding hand-related neural activity, both during movement preparation and execution, the beta (14–30 Hz) and mu (8–12 Hz) amplitude, decrease in amplitude (event-related desynchronization, ERD) over the motor cortex contralateral to the movement limb (Doyle, Yarrow, & Brown, 2005; Gladwin, Lindsen, & de Jong, 2006; Gladwin, ‘t Hart, de Jong, 2008; Pfurtscheller, Neuper, Pichler-Zalaudek, Edlinger, & Lopes da Silva, 2000; Poljac & Yeung, 2014; Stancá & Pfurtscheller, 1995). These movement-related amplitude asymmetries (MRAA) can be quantified according to the double subtraction rationale of the Lateralized Readiness Potentials in the time domain (LRP; Colebatch, 2007); by taking the difference in amplitude between contralateral and ipsilateral activity during preparation of right-hand response minus difference between ipsi- and contra-lateral activity during preparation of left-hand response (Gladwin et al., 2006). Given that the calculation of the MRAA eliminates motor-unrelated hemispheric lateralization, the remaining activity reflects motor-related preparatory lateralized activity. With repetitive alcohol use, cues associated with alcohol gain incentive salience and induce motivational responses (Robinson & Berridge, 1993, 2008). However, the process of preparing an action (approach/avoid) for conditioned cues with a specific affective connotation (alcohol vs. control cues, or positive vs. negative cues) requires mapping a motor response to a stimulus and in the case of approach tendencies this mapping is strengthened for approach responses on alcohol cues. Therefore both incentive motivations and pavlovian responses are likely to play a role in the approach bias. Compared to many other cognitive biases, stimulus-response associations are more central to approach tendencies, given that in this bias certain stimulus categories are inextricably linked with specific motor responses. To this end, studying MRAA indices allow us to differentiate tasks that require much skill and effort from automatically activated tasks; by comparing stimulus-response associations with different strengths. The first aim of the present study was to investigate the motor preparation in alcohol approach–avoidance bias by means of motor-related asymmetries as a function of drinking profile (light and heavy drinkers). Thus, we used a modified version of the AAT task that resembles the one used in our previous study (Korucuglu, Gladwin, & Wiers, 2014), extending it by focusing on lateralized spectral analysis. In our previous study, preparatory activity was measured by presenting a warning (or a preparatory) stimulus before the presentation of an imperative stimulus (S2) to which the subject had to give a motor response. Contrary to our previous study where right-hand joystick movement was required for response, the task used in this study consisted of trials requiring both left and right hand approach or avoid responses for alcohol-related and control cues to allow the study of motor-related lateralization.

In an earlier study, we showed that a low dose of alcohol administration increased the parietal beta-ERD during preparation for the alcohol-compatible trials (‘approach-alcohol/avoid-control picture trials’) following alcohol administration (Korucuglu et al., 2014), similar to facilitating effects of alcohol on appetitive processes (Duka & Townshend, 2004; Hodgson, Rankin, & Stockwell, 1979).

A second aim of the current study was to assess whether acute alcohol would enhance asymmetries associated with drug-related approach/avoidance motivations. Finally, we tested whether alcohol-induced effects on lateralized power spectra would be related to alcohol consumption, problems, and motivations; and would predict alcohol escalation in a young sample.

2. Methods

2.1. Participants

Forty adolescents (age range = 16–20 years) were recruited from local high schools in Amsterdam. Prior to the testing sessions, participants were informed about the study restrictions by email. Participants were required to be minimally 16 years-old (minimum drinking age in Netherlands at the time of the study), with a minimum weight of 50 kg and to have had at least one full drink in their lifetime. Participants were requested not to drink any alcohol 24 h before testing and eat a meal or drink caffeine 4 h prior to testing. Participants’ compliance with these restrictions was confirmed with self-report. Moreover, participants were instructed to abstain from any legal and illegal drugs for at least 1 week; their compliance with this restriction was confirmed with a urine test. Exclusion criteria were psychiatric disorders, diagnosed cases of drug use disorder, head trauma, seizures, severe physical illness, cardiovascular disease, chronic obstructive pulmonary disease, the presence of major medical conditions, and use of medication. Further exclusion criteria for female participants were pregnancy and breast-feeding; which were assessed with self-report.

Seven participants were excluded from data analysis (two due to a positive drug test for THC, two due to missing data in one session, one due to broken electrode, one due to being left handed, and one subject’s AUDIT score was missing), analysis was conducted with the remaining 33 participants. In this study we examined participants with light and heavy drinking patterns, drinking groups were formed by using an inventory on alcohol use and problems (Alcohol Use Disorder Identification Test, AUDIT) using a median-split (heavy drinking: AUDIT>8). All participants had normal or corrected-to-normal visual acuity. Prior to the experiment, written informed consent was obtained from all participants and from parents of participants under 18. The study was approved by the Ethical Committee of University of Amsterdam Psychology Department. Participants received financial compensation (Table 1).

2.2. Alcohol administration

All subjects participated in two sessions administered on two different days, between 2 to 7 days apart. Sessions started between 12:00 and 18:00 pm. Alcohol was administered in one session and placebo in the other. Dose order was counterbalanced across subjects. Participants were told that they would receive a different dose of alcohol during both sessions, to keep expectancy effects similar across sessions.

To keep the participants as well as the experimenter oblivious to the condition, a double blind procedure was used. Over-age subjects (18 year-olds and above) received a mix of vodka and orange juice. Under-age subjects (16 and 17 year-olds) received a vodka-orange premixed drink (Eristoff & Orange Can, commercial ready-to-drink alcoholic beverages with a 7% vol). The alcohol content and the total volume of the liquid delivered to the participants under and over the age of 18 were the same (0.45 g/kg with a maximum cut-off of 100 ml vodka). The mix was divided into three equal portions. Two of the drinks were served with 5 min apart, prior to commencing the task, and after electrode placement. Up to 3 min was allowed for drinking followed by 2 min of mouthwash to remove the residual alcohol in the mouth. In between the tasks 1/3 of the mix was administered as a booster drink in order to eliminate measurement during the descending limb of the BrAC. To enhance the alcohol taste, all the drinks had a lemon soaked in vodka and the glass in which drinks were served was sprayed with vodka beforehand. To mask the alcohol taste all drinks had three drops of tabasco sauce (McIlhenny Co., USA). The procedure was
identical in each session, except alcohol was replaced with orange juice in the placebo condition. Breath alcohol concentration (BrAC) was collected 5 min after the first two drinks, before and after the booster drink, and at the end of the experiment by using the Lion alcilometer® SD-400 (Lion Laboratories Limited, South Glamorgan, Wales). Participants filled out the Brief Biphasic Alcohol Effects Scale (B-BAES, Rüeger, McNamara, & King, 2009) each time a breath sample was taken, except before the booster drink. Throughout the experiment the BrAC was measured three times during which subjects also filled the B-BAES questionnaire: after alcohol administration, before the booster drink and at the end of the experiment. Moreover, an additional BrAC measurement was collected after the booster drink in order to monitor alcohol level following the top-up dose.

After completion of both sessions, a short manipulation check interview was conducted to determine whether the participants were aware of the alcohol contents of the drinks. Deception was not successful for one of the participants. Participants were debriefed about the true nature of the study and remained at the research site until their breath sample was 25 mg/100 ml or less.

2.3. Procedure

Upon arrival in the lab, participants filled out demographics, questionnaires related to personality and drinking habits. At the start of each session, participants completed the Desire for Alcohol Questionnaire (DAQ; Love, Es, & Willner, 1988) and the Positive and Negative Affect Scale (PANAS; Watson, Clark, Tellegen, 1988) to measure differences in current mood and alcohol across sessions. Current alcohol use and problems were assessed with the AUDIT (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993); we used both the standard past year version, and a version about the past 3 months. Motives to drink alcohol and drinking restraint were assessed with the Drinking Motives Questionnaire-Revised (DMQR-R; Cooper, 1994) and Temptation and Restraint Inventory (TRI; Collins & Lapp, 1992), respectively. Before and after alcohol administration, participants also performed other unrelated tasks (see Supplementary materials Fig. S2, for timeline of events). Order of the tasks was counterbalanced across participants, but was kept same across sessions for each subject. The data of the other tasks are not reported in this paper.

Each session took approximately two and a half hours, including breaks and the application of electrodes, during one afternoon. Six months after these two assessments, participants were contacted with e-mail for an online assessment on recent alcohol and drug use. If no response was received within a week, participants were contacted by phone. During follow-up assessment, participants filled out the same alcohol-related scales as during pre-test.

2.4. Alcohol approach avoidance task (A-AAT)

In the original A-AAT (Wiers et al., 2009) participants were instructed to pull (approach) or push (avoid) alcohol-related and control pictures by using a joystick. The EEG version of the AAT used in the current study was developed to compare the neural activity during preparation of alcohol approach and avoidance responses. Compared to the relevant-feature version used in our previous study (Korucuoglu et al., 2014), in this experiment the irrelevant-feature version of the task was used, where participants were presented with alcohol-related or soft-drink pictures in a portrait or landscape orientation with participants being instructed to approach or avoid pictures depending on the orientation of the picture (cf. Cousijn, Goudriaan, & Wiers, 2011).

The sequence of events in the trial was as follows (Fig. 1): The trial started with a fixation period (500 ms or 700 ms), followed by a preparation period. During the preparation period, the word
“Voorbereiden” ("prepare") was presented on top of the stimuli. Participants were instructed to prepare their response depending on the orientation of the picture (portrait or landscape) and instructions (pull or push by pressing the left or right button, assigned per block; see below for more details), and to withhold their response until the word disappeared. The word “Voorbereiden” was displayed centrally for a randomly selected amount of time between 1000 ms and 1500 ms with 100-ms increments. The stimuli remained on the screen until the response was given. After the response there was a zoom effect with a fixed duration of 500 ms. During this zoom effect, pulled pictures became bigger and pushed pictures became smaller. Participants received feedback only if the response was incorrect. Each picture was presented equally often in the portrait and landscape orientations. Since each picture (alcohol-related or soft-drink pictures) was presented in both orientations (left and right-tilted), the task consisted of four experimental conditions: (1) approach alcohol-related pictures, (2) avoid soft-drink pictures, (3) approach soft-drink pictures and (4) avoid alcohol-related pictures.

The task contained four blocks in total. In order to disentangle left/right hand and push/pull responses and allow motor-related asymmetry analyses, the assignment of the buttons (left or right hand side) to each action type (approach or avoid) alternated across blocks. For this reason, the sequence of block type during 4 experimental blocks followed either ABBA for half of the participants or BAAB design for the other half. During the block type A, the left button was assigned to the approach action and the right button was assigned to the avoid action. During the block type B, the mapping of left-right response buttons on action type was reversed. The contingencies of orientation (portrait or landscape) and the target action (pull or push) were randomized across participants in such a way that half of the participants were instructed to pull the pictures in portrait orientation and push pictures in landscape orientation and the other half received opposite instructions.

Each block started with 16 practice trials and was followed by 48 experimental trials. Non-beverage images (grey rectangles) were used during practice trials. During the first 6 practice trials in each block, the correct response was presented on top of the rectangles. Participants repeated a trial during practice block if the response was incorrect. To control for the effect of picture familiarity across sessions, two sets of pictures with and without alcohol contents were matched (12 alcohol-related and 12 control pictures, respectively.)
each presented equally often), and each stimulus set was randomly assigned to a session.

2.5. Behavioural data preparation

Practice trials and trials with incorrect response (i.e., a pull response in a push trial) were excluded from the behavioral data for RT analysis. RT was calculated from the end of the preparation period until the motor response. Due to the preparation period, responses were fast and no trials were excluded based on RT. Median RTs were analyzed as in previous AAT studies (e.g., Cousijn et al., 2011; Wiers et al., 2009).

2.6. Electroencephalogram (EEG) recording and data preparation

Electrophysiological data were recorded from the scalp using an Active-Two amplifier (Biosemi, Amsterdam, the Netherlands) from 32-scalp sites. Electrodes were placed at the standard positions of the 10–20 international system. Two electrodes were placed at the outer canthi of the eyes to measure horizontal eye movements. Two electrodes were placed at below and above the left eye to measure vertical eye movements. EEG was recorded at 2048 Hz sampling rate. The distance between the screen and the subject was kept at 75 cm.

EEG preprocessing was conducted using Brain Vision Analyzer (version 2.0, Brain Products GmbH, Munich, Germany). Data were down-sampled to 250 Hz, re-referenced offline to the average of left and right mastoids, low pass filtered at 50 Hz, and high pass filtered at 0.1 Hz. Ocular correction was applied using the algorithm of (Grafton, Coles, & Donchin, 1983). EEG data were segmented into 3 sec epochs starting 1s before the cue presentation to 2s afterwards. Trials were considered artefacts when the difference between consecutive data points was larger than 75 mV and the difference between the lowest and the highest voltage within a segment was higher than 200 mV. Epochs with an amplitude exceeding ±100 mV were excluded. After the exclusion of artefacts and noisy data, in the placebo condition an average of 38.39, 38.03, 38.18, 38.63 trials remained for subsequent analysis for the avoid soft, avoid alcohol, approach soft, and approach alcohol conditions, respectively. In the alcohol condition the numbers of remaining trials were 39.85, 39.21, 40.39, and 39.42, respectively for the avoid soft, avoid alcohol, approach soft, and approach alcohol conditions.

The Fieldtrip toolbox for EEG/MEG analysis was used for the time-frequency analysis (Oostenveld, Fries, Maris, & Schoffelen, 2011) running under Matlab 2010b. Because of their sensitivity to muscle activity, the (most) peripheral electrodes from left to right earlobes (Fp1, Fp2, F7, F8, T7, and T8) were excluded from further data analysis. Time-frequency was performed by convolving the time series with a family of Morlet Wavelets with a family ratio of (f0/σf=7), where f0 represent the frequency of interest. Frequencies of interest were alpha (8–12 Hz with 1 Hz frequency steps) and beta (13–30 Hz with 2 Hz frequency steps) frequency ranges. An absolute baseline correction was applied to the power spectrum by using the time period of −600 to −200 ms preceding the presentation of the cue.

2.7. Procedure to calculate bias scores and contrasts

Calculation of bias scores and contrasts are summarized in Table 2. First, cue-specific bias-scores were calculated separately for alcohol-related and soft-drink pictures by subtraction the median RT in pull trials from the median RT in push trials. Positive scores represent an approach bias and negative scores represent an avoidance bias. Similar to the calculation of bias scores, cue-specific MRAA bias-scores were calculated separately for alcohol and soft-drink cues by subtracting the MRAA in push trials from the MRAA in pull trials (i.e. MRAA alcohol bias-scores in placebo = MRAApull − MRAApush placebo-stimuli at T1 after placebo). Given that MRAA is calculated based on ERDs (decrease in activity), negative MRAA bias-scores represent relatively higher ERDs for the approach compared to avoid responses, and positive MRAA bias-scores represent relatively higher ERDs for the avoid compared to approach responses.

Brain-behavior relationship between MRAA scores and questionnaire was investigated with correlational analysis. For the purpose of this analysis, overall bias score was calculated for the MRAA data. For the calculation of overall bias, a double subtraction procedure was followed where the difference between the bias-score for the soft-drink and for the alcohol cues were calculated both for the MRAA data separately in the placebo and alcohol conditions (i.e. (MRAApull − MRAApush) alcohol-stimulus − (MRAApull − MRAApush) control-stimulus). In the placebo dose), Overall bias scores are MRAA differences between push and pull trials across alcohol-related and soft drink stimuli, note that this controls for general response bias due to a specific action (approach/avoid) or due to a specific stimulus category (alcohol/control cues). Therefore, negative overall MRAA bias-scores represent relatively greater alcohol-cue MRAA bias than soft-drink-cue MRAA bias and vice versa for the positive overall MRAA bias-scores.

Lastly, to study the predictive power of alcohol-induced effects on future drinking, dose-contrast scores, representing the difference between the alcohol and placebo conditions, were calculated both for the overall RT and the MRAA bias and used as predictors in the regression analysis.

2.7.1. Statistical analysis

All analyses were conducted using repeated measures ANOVA (RM-ANOVA) in SPSS. The Stimulation and Sedation subscales of B-BAES scores were separately analysed with Dose (Placebo, Alcohol), and Time (pre-task and post-task) as within-subjects factors. Similarly, the estimated blood alcohol levels (BAL) were subjected to RM-ANOVA, with time (BAL pre-AAT and BAL post-AAT) as within subject variable.

For the analysis of accuracy, RM-ANOVA was conducted with Dose (placebo, alcohol), Action (approach, avoid) and Stimulus Category (alcohol-related, soft-drink cues) as within-subject factors and Group (Light, Heavy drinkers) as between-subjects factor. The cue-specific bias scores were analyzed with Dose (placebo, alcohol) and Bias Type (alcohol-cue RT bias, soft-drink-cue RT bias) as within-subject factors and Group (Light, Heavy drinkers) as between-subjects factor. Note that for all the analysis conducted with RM-ANOVA, the cue-specific bias scores (difference between push-pull trials) were used, except for the accuracy and RT data we also presented results with Dose (placebo, alcohol), Action (approach, avoid) and Stimulus Category (alcohol-related, soft-drink pictures) as within-subject factors and Group (Light, Heavy drinkers) as between-subjects factor.

For the lateratization, statistical analysis was conducted with Dose (Placebo, Alcohol), and MRAA Bias-scores (alcohol-cue MRAA bias, Soft-drink-cue MRAA bias) as within-subject variables and Group (Light, Heavy drinkers) as between-subject variable, and for each time interval (T1:0–350 ms, T2:350–700 ms, T3:700–1000 ms) separately. Note that following earlier studies, the MRAA bias scores were analysed separately for early (T1), middle (T2) and late (T3) preparation intervals, because it was shown that preparatory activity in the frequency domain unfold over time (De Jong et al., 2006; Poljac & Yeung, 2014). In the Supplementary materials, we presented analysis showing an increase in motor preparation with the approaching response deadline (see section ‘desynchronization across timepoints’). The MRAA in different time intervals may represent quite different processes, and so even in the
Table 2  
List of variables used in the statistical analysis, their calculations and interpretations.

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Interpretation</th>
<th>Positive score</th>
<th>Negative score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cue-specific biases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol-cue RT bias</td>
<td>RT in push alcohol cue trials—RT in pull alcohol cue trials</td>
<td>Approach bias for alcohol cues</td>
<td>Avoid bias for alcohol cues</td>
</tr>
<tr>
<td>Soft-drink-cue RT bias</td>
<td>RT in push soft-drink cue trials—RT in pull soft-drink cue trials</td>
<td>Approach bias for soft-drink cues</td>
<td>Avoid bias for soft-drink cues</td>
</tr>
<tr>
<td>Alcohol-cue MRAA bias</td>
<td>MRAA in pull alcohol cue trials—MRAA in push alcohol cue trials</td>
<td>Relatively greater ERD for approach than alcohol cue response, i.e. avoid-related lateralization for alcohol cues</td>
<td>Relatively greater ERD for approach than alcohol cue response, i.e. approach-related lateralization for alcohol cues</td>
</tr>
<tr>
<td>Soft-drink-cue MRAA bias</td>
<td>MRAA in pull soft-drink cue trials—MRAA in push soft-drink cue trials</td>
<td>Relatively greater ERD for approach than soft-drink cue response; i.e. approach-related lateralization for soft-drink cues</td>
<td>Relatively greater ERD for approach than soft-drink cue response, i.e. approach-related lateralization for soft-drink cues</td>
</tr>
<tr>
<td><strong>Overall biases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall MRAA bias</td>
<td>Alcohol-cue MRAA bias—Soft-drink-cue MRAA bias</td>
<td>Relatively greater soft-drink-cue MRAA bias than alcohol-cue MRAA bias; i.e. greater lateralization for soft-drink bias</td>
<td>Relatively greater alcohol-cue MRAA bias than soft-drink-cue MRAA bias; i.e. greater lateralization for alcohol bias</td>
</tr>
<tr>
<td><strong>Contrasts capturing alcohol-induced effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT dose-contrast score</td>
<td>Overall RT bias in alcohol dose—Overall RT bias in placebo dose</td>
<td>Relatively stronger approach alcohol-cue RT bias score in alcohol dose than in placebo dose</td>
<td>Relatively stronger avoid alcohol-cue RT bias score in alcohol dose than in placebo dose</td>
</tr>
<tr>
<td>MRAA dose-contrast score</td>
<td>Overall MRAA bias in alcohol dose—Overall MRAA bias in placebo dose</td>
<td>Relatively stronger approach alcohol-cue MRAA bias score in alcohol dose than in placebo dose</td>
<td>Relatively stronger avoid alcohol-cue MRAA bias score in alcohol dose than in placebo dose</td>
</tr>
</tbody>
</table>

Variable in grey was not discussed in the paper due to lack of a statistical effect, but listed here only for the completeness. Movement-related amplitude asymmetry (MRAA) is quantified by taking the difference in amplitude between contralateral and ipsilateral activity during preparation of right-hand response minus difference between ipsi- and contra-lateral activity during preparation of left-hand response (Cladwin et al., 2006). Given that a decrease in power (ERD) is expected for the hemisphere contralateral to the movement, more negative MRAA values indicate greater motor-related lateralization due to increased ERD contralateral to the movement.

* List of variables used in repeated measures ANOVA.

* List of variables used in correlational analysis.

* List of variables used to test alcohol-induced effects as predictor of future alcohol escalation.

absence of significant interactions with the Time factor, we provide tests for each time interval separately. However, we acknowledge and emphasize that such effects must be considered exploratory.

Post-hoc comparisons were conducted by using paired sample t-tests while comparing task conditions (reported under ‘task effects per group’) and independent sample t-tests when comparing heavy vs. light drinkers.

2.7.2. Relationships between MRAA and individual differences
Correlations between overall MRAA bias score and alcohol-related problems/drinking motives (TRI/DMQR) were assessed with Pearson correlations.

2.7.3. Prediction of future drinking
In order to assess whether differences in RT bias-scores and MRAA bias-scores (for all three frequency bands) across sessions predicted unique variance in the change in alcohol use during the six months after the experiment, a hierarchical multiple regression analysis was conducted. First, behavioural measures (AUDIT score for recent use at baseline from the version about the past 90 days – sum of scores of items on frequency of drinking, typical quantity and frequency of heavy drinking –) were entered to the regression model, followed by the RT and MRAA dose-contrast scores (alcohol-induced changes in the RT and the MRAA). We focused on (1) whether alcohol effects on behaviour predicted change in alcohol use, and (2) whether alcohol effects on brain responses predicted alcohol use beyond the predictive value of behavioural measures.

3. Results

3.1. Manipulation checks
For the Stimulation and Sedation subscales of B-BAES scores, results revealed a significant main effect of Dose for the sedation subscale (F(1, 32) = 5.016, p = .032, η²p = .15). Sedation scores were higher for the alcohol dose compared to the placebo dose, however post-hoc analysis with paired t-tests did not reveal any differences across conditions. All other main and interaction effects were not significant (p > .15).

Three subjects’ post-task BrAC data were lost, the analysis was completed with the remaining participants. Results revealed that subjects performed the task during the steady state of alcohol level (p > .198) (see Table 3).

3.2. Accuracy
Accuracy data revealed a two-way interaction effect of Dose by Action Type (F(1, 31) = 5.874, p = .021). Post-hoc analysis with paired sample t-test revealed that compared to placebo, after alco-
hol administration participants made more errors in trials in which they had to avoid alcohol-related stimuli ($t(32) = −2.292, p = .029$).

### 3.3. Bias scores

The analysis of bias scores revealed a two-way interaction of Dose and Bias Type ($F(1, 31) = 6.602, p = .015, \eta^2_p = .176$). No interaction with the Group variable was observed. Participants demonstrated a non-significant positive alcohol-cue RT bias (approach bias for alcohol pictures) after a placebo dose and a positive soft-drink-cue RT bias (an approach bias for soft-drink pictures) after an alcohol dose. Post-hoc analysis revealed that after alcohol administration, soft-drink-cue RT bias scores tended to be higher compared to alcohol-cue RT bias scores, which did not reach significance ($t(32) = 1.816, p = .079$) (see Fig. 2, upper panel).

### 3.4. Reaction times

Reaction time data comparing all task conditions revealed a three-way interaction of Dose by Action Type and Stimulus Category ($F(1, 31) = 6.579, p = .015, \eta^2_p = .18$) and Stimulus Category by Group ($F(1, 31) = 4.48, p = .042, \eta^2_p = .13$) interaction effect. To follow-up three-way interaction of Dose by Action by Stimulus Category, we performed analysis separately for the placebo and alcohol dose. Results revealed a faster approach alcohol response compared to avoid alcohol response in the placebo condition ($t(32) = −2.1, p = .044$). To follow-up Stimulus Category by Group interaction, we collapsed the data across levels of Dose and Action variables. T-tests showed that overall heavy drinkers were faster for alcohol cues compared to soft drink cues, $t(14) = −2.879, p = .012$. No effect was observed for light drinkers. (see Fig. 2, lower panel).

### 3.5. Beta-MRAA bias

Beta MRAA bias scores are presented in Fig. 2 (top panel) for light and heavy drinkers. As can be seen, in the placebo condition light drinkers had positive alcohol-cue and soft-drink-cue MRAA bias scores representing avoid-related lateralization and heavy drinkers had negative alcohol-cue and soft-drink-cue MRAA bias scores representing approach-related lateralization for both cue types. In the alcohol condition, this pattern was reversed. The differences across groups were most prominent for the soft-drink-cue MRAA bias, especially in the placebo condition. We tested whether the positive avoid-related MRAA scores in heavy drinkers and negative approach-related MRAA scores in light drinkers were statistically different from each other and also across conditions. Analysis of the beta-MRAA revealed a Dose by Group interaction effect at early ($F(1, 31) = 7.927, p = .008, \eta^2_p = .204$), at middle ($F(1, 31) = 9.158, p = .005, \eta^2_p = .224$), and late periods ($F(1, 31) = 8.958, p = .005, \eta^2_p = .224$). At late preparation period, a significant Dose by Bias by Group ($F(1, 31) = 6.988, p = .013, \eta^2_p = .18$) and marginally significant Dose by Bias ($F(1, 31) = 3.987, p = .055, \eta^2_p = .144$) interaction effects were observed. To understand the nature of this three-way interaction, we conducted paired sample t-tests per group separately and independent samples t-tests to compare light and heavy drinkers.

#### 3.5.1. Task effect per group

At 700–1000 ms, after a placebo dose heavy drinkers’ negative MRAA soft-drink-cue bias-scores were different from the positive alcohol-cue MRAA bias-scores ($t(14) = 3.143, p = .007$). Also, for heavy drinkers at 700–1000 ms, negative soft-drink-cue MRAA bias-scores after a placebo dose were different from positive soft-
Fig. 3. MRAA.
Beta-, mu- and alpha-MRAA bias scores for three successive time points (T1: 0–350 ms, T2: 350–700 ms, T3: 700–1000 ms) following the presentation of the cue. ¥ indicates differences across placebo and alcohol conditions at p < .05. Note that bias scores are calculated, separately for alcohol and soft drink pictures, by subtracting MRAA scores for pull action from the MRAA scores for push action. Negative MRAA bias-scores represent relatively higher ERDs for the approach compared to avoid responses (similar to approach bias based on RT), and positive MRAA bias-scores represent relatively higher ERDs for avoid compared to approach responses (similar to avoid bias based on RT).


drink-cue MRAA bias-scores after an alcohol dose (t(14) = −2.641, p = .019). Light drinkers had negative soft-drink-cue MRAA bias-scores after an alcohol dose which was different than the positive soft-drink-cue MRAA bias-scores after a placebo dose at 0–350 ms (t(17) = 2.742, p = .014), at 350–700 ms (t(17) = 2.447, p = .026), and at 700–1000 ms (t(17) = 2.608, p = .022). Moreover, at 700–1000 ms, light drinkers had negative alcohol-cue MRAA bias-scores after an
alcohol dose which was different from the positive alcohol-cue MRAA bias-scores after a placebo dose ($t(17) = 2.527, p = .018$).

3.5.2. Heavy vs. light drinkers

At 0–350 ms, no differences were observed. At 350–700 ms and 700–1000 ms, after a placebo dose, heavy drinkers’ negative soft-drink-cue MRAA bias was different from light drinkers’ positive soft-drink-cue MRAA bias, (350–700 ms: $t(31) = 2.644, p = .013$; 700–1000 ms: $t(31) = 4.055, p < .001$). In the alcohol condition, light drinkers’ negative alcohol-cue MRAA bias was different from heavy drinkers’ positive alcohol-cue MRAA bias ($t(31) = -1.987, p = .056$) at 700–1000 ms.

3.6. Mu-MRAA bias

Mu MRAA bias scores are presented in Fig. 2 (middle panel) for light and heavy drinkers. As can be seen, both for alcohol and soft-drink cues, light drinkers had negative MRAA bias scores representing approach-related lateralization and heavy drinkers had positive MRAA bias scores representing avoidance-related lateralization, except for the late preparatory period where this pattern was reversed. Next we tested if the differences across heavy and light drinkers were statistically significant differences.

During the early preparation period (0–350 ms), analysis of the mu-MRAA bias revealed an interaction effect of Dose by Bias by Group ($F(1, 31) = 4.12, p = .051, \eta^2_p = 117$). During the middle preparation period (350–700 ms), Dose by Bias by Group was marginally significant ($F(1, 31) = 3.846, p = .059, \eta^2_p = .11$). During the late preparation period (700–1000 ms) a marginally significant Dose by Group interaction effect was observed ($F(1, 31) = 3.958, p = .056, \eta^2_p = 113$).

3.6.1. Task effect per group

No significant differences were observed across task conditions with pairwise t-tests conducted separately in heavy and light drinkers.

3.6.2. Heavy vs. light drinkers

Independent sample t-tests comparing heavy and light drinkers revealed that after an alcohol dose, light drinkers’ negative alcohol-cue MRAA bias-scores were different than heavy drinkers’ positive alcohol-cue MRAA bias-scores at 0–350 ms ($t(31) = -2.332, p = .026$) and 350–700 ms ($t(31) = -2.08, p = .046$). At 700–1000 ms, after an alcohol dose, light drinkers’ negative soft-drink-cue MRAA bias-scores were different from the heavy drinkers’ positive soft-drink-cue MRAA bias-scores ($t(31) = -2.178, p = .037$) (see Fig. 3).

3.7. Parietal alpha-MRAA bias

The parietal alpha revealed an interaction effect of Bias by Group at 0–350 ms ($F(31) = 6.284, p = .018, \eta^2_p = .169$) and an interaction effect of Dose by Group at 700–1000 ms ($F(31) = 4.374, p = .045, \eta^2_p = .124$).

3.7.1. Task effect per group

At 0–350 ms, after a placebo dose, light drinkers’ negative alcohol-cue MRAA bias-scores were different than the positive soft-drink-cue MRAA bias-scores ($t(17) = -3.008, p = .008$). At 700–1000 ms, positive soft-drink-cue MRAA bias-scores (representing greater avoid-related lateralization) after a placebo dose and the negative soft-drink-cue MRAA bias-scores (representing greater approach-related lateralization) after an alcohol dose were significantly different ($t(17) = 2.31, p = .034$).

3.7.2. Heavy vs. light drinkers

No differences were observed across groups.

3.8. Correlations

The Govern subscale of the TRI questionnaire (‘difficulty controlling alcohol intake’) positively correlated with the overall central beta-MRAA bias scores in the alcohol condition at 350–700 ms ($r = .34, p = .05$) and 700–1000 ms ($r = .43, p = .012$) and with the overall MRAA bias scores in the placebo condition at 700–1000 ms ($r = .37, p = .032$) (see Fig. 4). Individuals with higher TRI scores had more positive overall MRAA bias scores, and individuals with lower TRI scores had more negative overall MRAA bias scores.

3.9. Neural predictors of alcohol use after six months

Six months after the baseline assessment (alcohol challenge session), 82.5% follow-up response rate was achieved in the full sample of 40 participants. RT dose-contrast scores (depicting alcohol-induced changes on the overall RT bias scores) and the parietal alpha-MRAA dose-contrast scores at 350–700 ms (depicted alcohol-induced changes on the overall alpha-MRAA bias scores) predicted future alcohol use beyond the variance explained by baseline AUDIT scores. The total variance explained by the full model was 81.5% ($F$-change$_{1,24} = 5.903, p = .023$).
The baseline AUDIT scores explained 70.5% of the variance (F-change$_{1,26}$ = 62.103, p < .001). RT dose-contrast scores and the parietal alpha-MRAA dose-contrast scores explained an additional 6.4 and 4.6% of the variance (F-change$_{1,25}$ = 6.931, p = .014; F-change$_{1,25}$ = 5.903, p = .023) (see Fig. 5). To follow up, a correlation analysis between change in AUDIT scores (AUDIT$_{follow-up}$ - AUDIT$_{baseline}$) and the predictors of the change in alcohol use was conducted (the RT and the parietal alpha-MRAA dose-contrast scores). Individuals who had relatively more negative overall bias scores for the RT after alcohol administration at baseline (due to a stronger approach soft-drink and weaker approach alcohol bias, as depicted in Fig. 5b), had lower Audit scores, 6 months later (r = .384, p = .044). Follow-up correlations for the parietal-MRAA dose-contrast scores did not reveal significant effects.

4. Discussion

In the current EEG study, we focused on motor-related lateralization during preparation for approach and avoidance behaviors in the context of alcohol cues and investigated the effects of a prime dose of alcohol on these neurophysiological measures in heavy and light drinking adolescents. As in previous studies of motor preparation, preparation of a left/right hand response during the alcohol approach-avoidance task led to an MRAA following the presentation of the imperative stimulus (Supplementary materials, Fig. S1). This preparatory MRAA was found to be related to experimental conditions and drinking behavior. Behavioural results revealed faster responses for approaching alcohol-related cues compared to avoiding alcohol ones in the placebo condition. After alcohol, a non-significant decrease was observed for approach alcohol bias, especially in heavy drinkers. A relatively strong approach soft-drink and weak approach alcohol reaction-time bias after alcohol predicted decreasing drinking; suggesting that the capacity to modulate an alcohol-approach bias while under the influence of an alcohol dose could be a protective factor. In heavy drinking adolescents increased approach-related asymmetry in the beta-band was observed for soft-drink cues compared to alcohol ones and this increase was associated with an increase in difficulty in regulating alcohol intake. Possible implications of this effect on the interpretation of the MRAA are discussed below.

In earlier studies, the mu- and beta-MRAA indices have been studied with switch task, pre-cueing RT paradigm, and motor imagery task (De Jong et al., 2006; Deiber et al., 2012; Doyle et al., 2005; Gladwin et al., 2008; Gladwin et al., 2006; Nam et al., 2011; Poljac & Yeung, 2014). During task switching paradigms (subjects need to switch their response hand when the current task switches), a reversal of lateralization of the mu and beta-MRAA from previous to current task set has been observed (De Jong et al., 2006; Gladwin et al., 2006; Poljac & Yeung, 2014), suggesting that MRAA reflects selection of motor goal and advance task preparation. This interpretation is strengthened by the finding of higher beta-band MRAA in 100% informative cues compared to 50% informative one (Doyle et al., 2005). In this study visuospatial attention to the imperative cues was also measured and it was found to be unrelated to the magnitude of the MRAA index. However, in another pre-cueing RT task, a cento-parietal alpha-MRAA was found to be reflecting visuospatial attention (Deiber et al., 2012). This study revealed a spectral pattern for weak lateralizers suggesting the recruitment of more visuospatial attentional resources (alpha ERD) and for high lateralizers suppression of irrelevant visual activity (alpha event-related synchronization, ERS).

Based on earlier findings, we expected that heavier drinkers would show an increased (more negative) mu- and beta-MRAA index for the approach versus avoidance alcohol-related cues

---

**Fig. 5. Predicators of alcohol use.**

(a) Hierarchical multiple regression analysis for variables predicting AUDIT at 6-month follow-up (n = 28). (b) Scatterplots between change in AUDIT scores (AUDIT$_{follow-up}$ - last 90 days - AUDIT$_{baseline}$, last 90 days) and (from left to right) alcohol-induced changes in the overall RT bias (alcohol minus soft-drink cue RT bias) and alcohol-induced changes on alcohol-cue and the control-cue (soft-drink-cue) RT bias, separately.
compared to soft-drink cues, representing advance response preparation for these trial types. In heavy drinkers, greater approach-related lateralization was observed for approach soft-drink cues especially during the late preparation period, suggesting an increased asymmetry index for the bias in the direction opposite to the one hypothesized. The effects for the mu- and alpha-MRAA bias scores were found to be in the same direction, higher lateralization of the ERD for soft-drink bias in heavy drinkers. For the alpha and the mu, differences across conditions were moderate and did not lead to significant results. An exploratory analysis also performed on behavior indicated that increased approach alcohol reaction (compared to avoidance reaction) was more pronounced in heavy drinkers ($p < .05$). Given that heavy drinkers had a greater approach bias for alcohol cues and also greater lateralization for approaching soft drink; the findings of the current study suggest that the asymmetry index measured with the AAT is likely to reflect an effortful response preparation process rather than an automatic advance response preparation. This could be due to two reasons: first, a lack of lateralization for approach alcohol response might represent the presence of an automatic response bias. However, another likely scenario is a possible relationship between behavior and lateralization, which resembles the “speed-accuracy” tradeoff for perceptual tasks. In the present case, our heavy drinking participants showed faster responses for approaching alcohol stimuli (compared to avoiding alcohol pictures) after placebo administration, however, they lacked approach-related lateralization for alcohol-related stimuli in the brain. In line with this, for the soft-drink stimuli an increased lateralization was observed for more effortful approach behavior. In sum, rather than a lack of lateralization possibly meaning an automatized process, the presence of lateralization could reflect effortful processing to overcome preexisting response preferences. Also our correlational analysis revealed that individuals with greater difficulty in regulating their drinking (note that heavy drinkers had greater difficulty), had greater approach-related lateralization for soft-drink cues and individuals with less problem with control over drinking had greater approach-related lateralization for alcohol cues. Using an alcohol implicit association test (IAT), it has been shown that young heavy drinkers hold both positive and negative alcohol associations (Houben & Wiers, 2006), most likely reflecting ambiguity towards alcohol. Therefore, a likely explanation for the MRAA pattern in heavy drinkers is that problems in controlling alcohol intake may have caused ambivalence in these individuals, and subjects may have compensated for this ambiguity by putting more effort in preparing their response for trials incongruent with their state of drinking profile (approaching soft-drink cues).

Based on earlier findings of alcohol's priming effects on cognitive biases in adult samples (Field, Schoenmakers, & Wiers, 2008), one may expect acute alcohol to increase this bias. However, earlier studies failed to show such an effect on RT with a relevant-feature version of the task with explicit instructions to approach/avoid alcohol-related cues (Korucuoglu et al., 2014; Schoenmakers et al., 2008). Results of the current study employing an irrelevant-feature version of the task demonstrated that after alcohol, the bias for the alcohol cues decreased especially in heavy drinkers. With alcohol administration, while heavy drinkers slowed down their responding for approach alcohol and avoid soft-drink cue trials (this could be due to a decrease in inhibition or an increase in distraction), light drinkers showed a non-significant decrease in response time during approach soft-drink and avoid alcohol cue trial types. However, this difference between groups was not significant, and thus the direction of this effect can only be tentatively interpreted. Moreover, regression analysis revealed that individuals who had a relatively strong avoid alcohol bias after alcohol administration during the alcohol challenge (due to a stronger approach soft-drink and a weaker approach alcohol bias), had lower Audit scores, six months later. The evidence in this study suggests that the ability to respond adaptively under the influence of alcohol can be a protective factor for the development of addictive behaviours. Earlier studies showed that if alcohol is consumed in the presence of conditioned cues (drug-related environmental cues), individuals are able to counter the effects of alcohol on cognitive function (Birak, Terry, & Higgs, 2010; Birak, Higgs, & Terry, 2011), suggesting a cognitive tolerance to drugs in the presence of drug cues. It is important to note that these results might be specific to irrelevant version of the task used here, given that the implicit nature of the instructions probably gave more room for the top-down influence of task instructions on performance.

To conclude, results revealed greater preparatory approach-related lateralized activity for approach soft-drink cues in heavier drinkers in comparison to light drinkers and also in comparison to lateralization for the alcohol cues. The beta-lateralization measured in this study may represent a compensatory effort for the weaker S–R mapping in heavy drinkers. The extent of alcohol-induced changes on the bias were related to changes in alcohol use, suggesting that the capacity to control the bias under alcohol could be a protective factor. It is important to note here, heavier drinkers in the present study also reported greater problems with controlling their drinking behavior. Studies with preselected samples can be considered to compare lateralization index in heavy drinkers with and without problems to control their drinking levels. Also future studies with a larger sample can focus on asymmetry differences between heavy drinking individuals who can and cannot overcome their approach alcohol bias.

Conflict of interest

All authors declare that they have no conflict of interest.

Acknowledgements

The authors are supported by VICI award 453.08.01 from the Netherlands National Science Foundation (N.W.O.). Thomas E. Gladwin is supported by ERAB grant EA 1239.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.biopsych.2015.12.012.

References


Wiers, R. W., Ebel, C., Rinck, M. Becker, E. S., & Lindenmeyer, J. (2011). Retraining automatic action tendencies changes alcoholic patients’ approach bias for alcohol and improves treatment outcome. Psychological Science, 22(4), 490–497. http://dx.doi.org/10.1177/0956797611400615