Acute alcohol effects on conditioned pain modulation, but not temporal summation of pain

Claudia Horn-Hofmann, Eva Susanne Capito, Jörg Wolstein, Stefan Lautenbacher

Abstract

Although pain reduction after alcohol administration has repeatedly been demonstrated, alcohol effects on advanced and clinically relevant dynamic pain paradigms are still unknown. As such, temporal summation of pain (TSP) and conditioned pain modulation (CPM) indicate mechanisms of endogenous pain modulation and involve certain neurotransmitter systems crucially influenced by alcohol. Our study is the first to investigate acute alcohol effects on TSP and CPM. We investigated 39 healthy subjects in a placebo-controlled within-subject design and targeted alcohol levels of 0.06% (dose 1) and 0.08% (dose 2). Pain threshold, TSP, and CPM were evaluated before and after an alcoholic or placebo drink. Temporal summation of pain was assessed as enhanced pain response to 5 repetitive contact heat stimuli (threshold +3°C). Conditioned pain modulation was tested as pain inhibition when a conditioning stimulus (46°C hot water) was applied concurrently to a test stimulus (contact heat; threshold +3°C). Both alcohol doses boosted CPM, with a greater effect size for the higher dose. Conditioning stimulus ratings increased after alcohol intake but were not correlated with CPM, suggesting independence of these effects. Temporal summation of pain was not affected by alcohol, and alcohol effects on pain threshold were small and limited to the higher dose. Our findings suggest that analgesic alcohol effects might be mainly driven by an enhancement of endogenous pain inhibition. The frequent use of alcohol as self-medication in chronic pain might be motivated by alcohol temporarily restoring deficient CPM, thus leading to pain relief in the short run and alcohol-related problems in the long run.

Keywords: Alcohol effects, Analgesia, Endogenous pain modulation, Temporal summation of pain, Conditioned pain modulation

1. Introduction

The belief in pain-relieving properties of alcohol dates back to antiquity and is still common considering the frequent self-medication by alcohol in individuals with chronic pain. However, causal evidence for analgesic effects of alcohol is only provided by experimental research, which has been recently reviewed twice. A total of 23 studies suggest dose-dependent analgesic effects of alcohol. The reviewed studies, however, were mainly published more than 30 years ago and limited to pain threshold, pain tolerance, and pain ratings. Alcohol effects on dynamic pain paradigms such as temporal summation of pain (TSP) and conditioned pain modulation (CPM) have not yet been examined. These dynamic paradigms capture the inhibitory (CPM) and excitatory (TSP) side of endogenous pain modulation and have seemed to be associated with clinical pain. Temporal summation of pain is an experimental correlate of the electrophysiological wind-up phenomenon in the dorsal horn and is characterized by enhanced pain responses to repetitively presented noxious stimuli (critical rate > 0.3 Hz). Conditioned pain modulation is regarded as psychophysical correlate of the “diffuse noxious inhibitory controls” (DNIC) mediated by a spinobulbospinal loop; it describes the attenuated response to a test stimulus (TS) when concurrently applied with a second noxious stimulus, the conditioning stimulus (CS).

The investigation of TSP and CPM seems mandatory, given that alcohol affects several important neurotransmitter systems also involved in endogenous pain modulation. Temporal summation of pain is evidently driven by sensitized N-methyl-D-aspartate (NMDA) glutamate receptor activation and alcohol acts as a potent NMDA receptor inhibitor. Animal and human studies suggest an involvement of the serotonergic and opioid systems in DNIC/CPM, which are both enhanced by alcohol. Thus, alcohol might exert antinoceptive effects by weakening the excitatory side (ie, TSP) and/or enhancing the inhibitory side (ie, CPM) of pain modulation.

Besides its analgesic action, alcohol may also influence mood, which requires consideration as indirect influence on pain. In consequence, both the sensory and affective dimensions of pain—commonly assessed by ratings of pain intensity vs pain unpleasantness—deserve attention. Previous research has shown that emotional influences preferentially modulate the affective dimension of pain. Therefore, stronger alcohol effects on the affective dimension might suggest a moderating role of emotional processes. In accord, 2 studies provided weak evidence for stronger alcohol effects on unpleasantness than intensity ratings.

Based on these considerations, our study aimed at investigating for the first time alcohol effects on TSP and CPM.
with supposedly dampening the excitatory and enhancing the inhibitory system, (2) evaluating differential effects of alcohol on intensity vs unpleasantness ratings, assuming more action on the affective dimension, and (3) replicating previous alcohol effects of an increase in pain threshold. Two subtoxic alcohol doses (target alcohol levels: 0.06%, 0.08%) were applied in a placebo-controlled double-blind within-subject design with 3 balanced sessions per participant. Pain parameters were assessed twice in each experimental session, before and after drinking an alcohol or a placebo mixture.

2. Materials and methods

2.1. Subjects

Participants were recruited through announcement in the local media. Exclusion criteria were regular intake of analgesics and prescription drugs (except oral contraceptives), severe acute or chronic illness, any disorders including pain symptoms, use of illegal substances, and alcohol use disorders. Female subjects had to provide a negative pregnancy test; mothers still breastfeeding were not allowed to participate. We investigated a total of 40 healthy individuals aged between 30 and 60 years who reported drinking moderate doses of alcohol at social occasions (social drinkers). One male subject was excluded from further analyses due to screening positive for depression (see 2.5.1). Thus, our final sample comprised 39 participants (20 female; age total: M = 46.6, SD = 8.8 years, age female: M = 46.0, SD = 8.5 years, age male: M = 47.2, SD = 9.3 years). The experiment was approved by the ethics committee of the medical department of the University Erlangen-Nuremberg. All participants provided written informed consent and received monetary compensation for their participation.

2.2. Procedure

Each of the 3 test sessions lasted for about 2.5 hours and consisted of 2 pain testing blocks that were conducted before (T1) and after (T2) the drink administration block. In addition, there was a short measurement block before pain assessment consisting of an initial measurement of breath alcohol concentration (BrAc), a 10-minute reaction time task (see 2.6), and the determination of participants’ body weight. The experimental procedure (Fig. 1) was identical in the 3 sessions except for screening instruments, which were administered only at the beginning of the first session as well as pain-related trait questionnaires, which were administered only at the end of the placebo session (Fig. 1 and 2.5). Breath alcohol concentration was assessed at 4 time points throughout the experiment (Fig. 1 and 2.3). In addition, the German short version of the Profile of Mood States (POMS) was administered at 4 time points to track changes in mood (Fig. 1 and 2.5). To assure blinding of the experimenter, the few measurements before pain assessment and the drink administration were conducted by a student assistant in an adjacent room (Fig. 1; left side). At the end of each experimental session, we verbally assessed participants’ beliefs regarding the nature of the condition (alcohol or placebo) before the final BrAc measurement (“Do you think you have received alcohol in this session?”).

The order of conditions (placebo, dose 1, and dose 2) was balanced across participants, and the 3 sessions were separated by 1 to 6 days. All sessions took place in the afternoon in 2 rooms (experimental laboratory and adjacent room) of the Department of Physiological Psychology at the University of Bamberg.

Participants were asked to refrain from smoking one hour, from food intake 4 hours, and from consumption of alcohol and any other drugs (except for oral contraceptives) 24 hours before attending the test sessions. After completing the third test session, subjects were fully debriefed regarding the study aims.

2.3. Drink administration and breath alcohol concentration measurements

A nonalcoholic cocktail consisting of lime juice (20 mL), blue curacao syrup (40 mL), and bitter lemon (120 mL for the placebo drink, 120 mL minus the individually calculated amount of alcohol for the alcoholic drink) served as basis for the administered drink. Ethyl alcohol (70% vol.) was added to the drink in both alcohol conditions and was used to spray the rim of the glass in the placebo condition to mimic the alcoholic scent. Participants received 2 glasses (200 mL) of the cocktail successively. Each glass had to be consumed within 5 minutes. Ten minutes after consumption of each glass, BrAc measurements were taken

![Figure 1](https://via.placeholder.com/150)

**Figure 1.** Illustration of the experimental paradigm. Dotted lines indicate assessments which took place in only one of the experimental sessions (screening: only first session; pain questionnaires: only placebo session). AUDIT, Alcohol Use Disorder Identification Test; BDI, Beck Depression Inventory; BrAc, breath alcohol concentration; CPM, conditioned pain modulation; POMS, Profile of Mood States; SCID, Structured Clinical Interview for DSM Disorders.
regardless of whether participants were in the alcohol conditions or in the placebo condition. In the alcohol conditions, the BrAc value measured after consumption of the first glass (BrAc 2) was used to adjust—if necessary—the amount of alcohol to be administered in the second glass.

The amount of alcohol administered to participants was calculated by using the Widmark Formula: \[ c = \frac{A \cdot m \times r}{M} \]
whereby \( c \) represents the target BrAC value (dose 1: 0.06%, dose 2: 0.08%), \( A \) is the amount of alcohol (mL), \( m \) is the subject's weight (kg), and \( r \) is the distribution factor (0.7). The resulting value for \( A \) was divided between the 2 glasses so that the first glass contained 75% and the second glass contained 25% of the total dose in case of BrAc 2 values ≥75% of the target value (i.e., 0.045% for dose 1 and 0.06% for dose 2). In case of BrAc 2 values <75% of the target value, the difference to the target value was added to these 25% to prevent large variation regarding BrAcs, which might be caused by interindividual differences in alcohol metabolism. This procedure was adapted from a previous study.65

Breath alcohol concentrations were measured with a breathalyzer (DRÄGER Alcotest 7410Plus, Dräger Medical GmbH, Lübeck, Germany) at four time points throughout each session (Fig. 1): At the beginning of the session (BrAc 1) to assure that participants were sober (BrAc = 0.00%) on arrival; (2) 10 minutes after ingestion of the first glass (BrAc 2); (3) 10 minutes after ingestion of the second glass (BrAc 3), which is immediately before T2 pain testing; and (4) at the end of each session (BrAc 4) before participants returned home. Participants were informed of the result of the BrAc 4 measurement and in case of values ≥0.03%, they were recommended to stay in the hallway outside adjacent to our laboratory until a value of <0.03% was reached. In this case, BrAc was reassessed in 20-minute intervals until the target value was reached and the participant was sent home.

2.4. Pain testing
2.4.1. Procedure
The pain testing block, which was conducted twice in each session (T1, T2; Fig. 1), consisted of (1) the determination of pain threshold, and (2) 2 runs of a TSP paradigm whereby the first run served as baseline condition (without CS) and the second run served as CPM condition (with CS). Otherwise, the paradigm (see 2.4.4 for a more detailed description) was identical in both runs and consisted of 3 single stimuli and 3 series of stimuli that were applied in an alternating sequence. Participants rated pain intensity and unpleasantness after each stimulus.

2.4.2. Apparatus (stimulators)
Contact heat stimuli were generated and applied by a computer-controlled contact heat-evoked potential stimulator (CHEPS, Medoc, Israel) with a round 27-mm diameter surface thermode for pain threshold assessment and phasic stimulation (TSP, TS in CPM). A pair of thermocouples is embedded in the lamina of the thermode surface, which allows for the assessment of the skin temperature at the stimulated area. The thermode was applied to the volar side of the left forearm.
Hot-water tonic stimulation for CS in CPM was provided by a circulating water bath (Wisecircu WCB-11; Witteg GmbH, Wertheim, Germany). The water temperature was set to 46°C based on the results of previous studies.25,63 The participant immersed her/his right hand up to 2 cm above the wrist in the water bath for the complete duration of the CPM condition. The water temperature was controlled by a thermostat, and the water was stirred with a force and suction pump to avoid layers of lower temperature around the hand.

2.4.3. Pain threshold assessment
Pain threshold was determined using the method of limits. Thermode temperature increased from a baseline of 35°C with a rate of 0.7°C/second until the participant perceived a first sensation of pain and pressed a stop button. Then, the temperature returned with a rate of 2°C/second to the constant baseline temperature until the next trial; interstimulus intervals varied from 9 to 11 seconds. There were 8 trials altogether; the first 3 trials were used as practice trials and the remaining 5 were used to determine the threshold estimate.

2.4.4. Temporal summation of pain paradigm
As stated above, both runs of the TSP paradigm were identical (despite presence or absence of the CS) and consisted of 3 single stimuli and 3 series of stimuli. The intensity of the stimuli was tailored to each individual's pain threshold + 3°C because this intensity has proven to elicit a moderately painful sensation and reliable TSP in previous studies.25,34 Stimulus intensity was always based on the preceding pain threshold assessment (T1 intensity = T1 threshold + 3°C, T2 intensity = T2 threshold + 3°C). All stimuli had a baseline temperature of 35°C that was held constant between stimuli. Temperature increased with a rate of 10°C/second and decreased with a rate of 10°C/second. Plateau duration of all stimuli was 0.1 second. Three single pulses and 3 series of 5 pulses (repetition frequency 0.5 Hz) were alternately presented with interstimulus intervals of 45 seconds (single pulse to train of pulses) and 57 seconds (train of pulses to single pulse), resulting together with the duration of stimulation in a total duration of 5.5 minutes.

2.4.5. Ratings
After the application of each single stimulus and after each series of stimuli, participants were asked to verbally rate the perceived intensity and unpleasantness on 2 numerical rating scales ranging from 0 ("not painful/unpleasant") to 10 ("extremely painful/unpleasant"). In case of the series of stimuli, only the last stimulus had to be rated. There were 2 rating practice trials (one with a single stimulus and one with a series of stimuli) at the beginning of the baseline condition in each session. In the CPM conditions, participants additionally rated the perceived intensity and unpleasantness of the water bath (CS) immediately after the ratings of the contact heat stimuli.

To avoid confounding of TSP and CPM effects, only ratings within the baseline condition were considered for the analysis of alcohol effects on TSP, and only ratings of single stimuli were considered for the analysis of alcohol effects on CPM (see 2.7).

2.5. Self-report measures
2.5.1. Screening instruments
At the beginning of the first session, participants were screened for problematic alcohol use and depression by use of the German versions of the Alcohol Use Disorders Identification Test (AUDIT)25,15 and the Beck Depression Inventory (BDI).7,20 Participants scoring above the cutoff of 9 in the AUDIT were additionally screened for alcohol abuse and addiction by use of the
Structured Clinical Interview for DSM Disorders (SCID interview). If their answers indicated potential alcohol abuse, they were excluded from participation, however, this applied to none of the participants. Participants scoring above 19 in the BDI (indicating moderate to severe depression) were excluded from participation; this applied to one male participant.

### 2.5.2. Assessment of mood

Changes in mood were tracked using the German short version of the Profile of Mood States Questionnaire (POMS). This version of the POMS contains a list of 35 adjectives describing affective states, and participants are asked to indicate by rating each item on a 7-point scale the current intensity of the respective feeling (0 = not at all; 6 = very strongly). It consists of 4 subscales, each indicating different facets of negative affect (depression/anxiety, fatigue, hostility, and vigor). For further analyses, we used the combined sum score of the POMS (range: 0-210), which can be interpreted as a global measure of negative affect.

Participants completed the POMS at 4 time points throughout the experiment (Fig. 1). Because we were mainly interested in mood changes due to consumption of the alcoholic or placebo beverage, we focused on the comparison between POMS2 and POMS3, which were assessed immediately before and immediately after drink administration, respectively.

### 2.5.3. Pain-related trait questionnaires

Pain-related cognitions and emotions were assessed by use of the German versions of the Pain Vigilance and Awareness Questionnaire (PVAQ), the Pain Catastrophizing Scale (PCS), and the Pain Anxiety Symptoms Scale (PAS). These questionnaires were always administered at the end of the placebo session to (1) prevent priming of negative thoughts relating to pain before pain testing, and (2) assure that participants were sober when completing the questionnaires.

Pain Vigilance and Awareness Questionnaire, PCS, and PASS have been repeatedly used in our laboratory with sufficient psychometric similarity to the original English versions as regards internal consistency and intercorrelations between scales.

### 2.6. Reaction time task

A simple reaction time task with (duration: 10 minutes) was conducted at 3 time points in each experimental session: at the beginning and after each of the 2 glasses. Participants had to indicate the color of a circle appearing on the middle of the screen (red or blue) as quickly as possible by a button press on a 2-button response panel. This task was mainly included to keep participants occupied during the 10-minute waiting period after consumption of each glass and thus prevent them from focusing excessively on potential bodily symptoms caused by alcohol intake. Results of this task are not reported here.

### 2.7. Data reduction and analysis

Within each of the phasic stimulation conditions, ratings were averaged across the 3 single stimuli and the last stimuli of the 3 series of stimuli separately for the both pain dimensions (intensity and unpleasantness) before subjecting them to further analysis. Ratings of the tonic CS (hot water) were averaged across the 6 assessments within each of the CPM conditions and then subjected to further analysis. In addition, CPM scores (ratingbaseline – ratingCPM) were computed as a measure for the size of the CPM effect.

As manipulation check, the administered alcohol doses and BrACs measured after the second glass (BrAC2) were compared between the 2 alcohol conditions using dependent samples t-tests. In addition, subjective beliefs concerning the nature of the condition (alcohol or placebo) were descriptively compared between conditions.

Alcohol effects on the pain measures (threshold, CPM, and TSP) were evaluated by using repeated-measurement analyses of variance (ANOVAs) with the following within-subject factors: (1) pain threshold: “condition” (placebo, dose 1, dose 2) × “pre-post” (T1, T2); (2) TSP: “condition” (placebo, dose 1, dose 2) × “pre-post” (T1, T2) × “TSP” (single stimuli, series of stimuli); and (3) CPM: “condition” (placebo, dose 1, dose 2) × “pre-post” (T1, T2) × “CPM” (baseline, CPM). To keep these analyses as simple as possible, alcohol effects on TSP were tested solely based on ratings in the baseline condition, and alcohol effects on CPM were tested solely based on ratings of single stimuli. For both TSP and CPM, we considered only ratings of pain intensity.

To investigate alcohol effects on pain intensity vs Unpleasantness, we conducted a repeated-measurement ANOVA with the within-subject factors “condition” (placebo, dose 1, dose 2), “pre-post” (T1, T2), and “dimension” (intensity, unpleasantness). This analysis was based solely on ratings of single stimuli in the baseline condition to avoid confounding by TSP and CPM effects.

Effects of alcohol on CS ratings were explored by a repeated-measurement ANOVA with the within-subject factors “condition” (placebo, dose 1, dose 2) and “pre-post” (T1, T2). Associations between CS ratings and the size of the CPM effect (raw values and pre-post changes) were analyzed using a correlation analysis.

Alcohol effects on mood were evaluated by computing a repeated-measurement ANOVA with the within-subject factors “condition” (placebo, dose 1, dose 2) and “pre-post” (T1, T2). This analysis was based on the POMS scores assessed immediately before and immediately after drink administration (POMS2 and POMS3).

T-tests were computed for detailed post hoc analyses. Adjusting degrees of freedom with Greenhouse–Geisser correction was necessary in case of violation of sphericity. For F-tests, partial eta squared (ηp²) (0.01: small effect; 0.06: medium effect; and 0.14: large effect) is reported as an estimate of effect size; Cohen’s d (0.20: small effect; 0.50: medium effect; and 0.80: large effect) is reported to describe effect size for paired comparisons. The alpha level was set to 5% for significance testing. SPSS 25 (IBM) was used for all calculations.

### 3. Results

#### 3.1. Descriptive sample characteristics

Descriptive statistics of questionnaire scores and body weight are provided in Table 1. None of the participants reported any DSM IV-relevant indicators of risk alcohol abuse or addiction, and BDI scores were—after the exclusion of one participant scoring above the cutoff (see 2.5.1)—within the norm values for nonclinical samples. Pain Anxiety Symptoms Scale, PCS, and PVAQ scores were comparable with those of other nonclinical samples.

#### 3.2. Manipulation check

As expected, BrAC was 0.00% in the placebo condition across all measurements. Mean values of BrAC after the second glass (BrAC2) (dose 1: M = 0.050%, SD = 0.012; dose 2: M = 0.071%).
SD = 0.012] were significantly higher for dose 2 than for dose 1 (t[38] = 7.86, P < 0.001, d = 1.77). The same applied to the administered total alcohol dose (dose 1: M = 72.26 g, SD = 12.85; dose 2: M = 96.30 g, SD = 17.21; t[38] = 33.34, P < 0.001, d = 0.41) and relative to the participant's weight (dose 1: M = 0.94 kg/kg, SD = 0.01; dose 2: M = 1.25 kg/kg, SD = 0.02; t(38) = 115.69, P < 0.001, d = 18.82). In the placebo condition, 38.5% of the participants (N = 15) believed that they had received an alcoholic drink, thus proving that we were successful in inducing uncertainty regarding the content of the drink in this condition. By contrast, almost all participants were sure that they had received alcohol in the alcohol conditions (dose 1: 89.7%, N = 35; dose 2: 97.4%, N = 38).

3.3. Alcohol effects on pain measures

For pain threshold, the ANOVA yielded a significant main effect of "condition" (F[2,76] = 3.653, P = 0.031, η² = 0.068); threshold was significantly higher in the dose 2 condition compared with the placebo condition (placebo: M = 45.15°C, SD = 1.51; dose 2: M = 45.55°C, SD = 1.64; t(38) = 2.848, P = 0.007, d = 0.25). In addition, there was a trend towards a significant "condition" × "pre-post" interaction (F[2,76] = 2.02, P = 0.067, η² = 0.069); threshold descriptively decreased from T1 to T2 in the placebo condition (M₀₂ - T₁ = −0.15, SD = 0.88) and in the dose 1 condition (M₀₂ - T₁ = −0.12, SD = 0.96) but increased in the dose 2 condition (M₀₂ - T₁ = 0.26, SD = 1.15) (see Table 2 for descriptives). There was no significant main effect of "pre-post" (F[1,38] = 0.001, P = 0.976, η² < 0.001). Thus, as regards pain thresholds, the effect of alcohol seemed to be weak and notable only after dose 2.

For TSP, the ANOVA yielded a highly significant main effect of "TSP" (F[1,38] = 113.076, P < 0.001, η² = 0.748), indicating overall higher ratings for series of stimuli compared with single stimuli (Table 2). The application of the series increased the pain rating approximately by one scale unit (1/10). There were no significant main effects of "condition" (F[2,76] = 1.558, P = 0.217, η² = 0.039) or "pre-post" (F[1,38] = 2.330, P = 0.135, η² = 0.058) and also no significant interaction (F[2,76] = 0.786, P = 0.459, η² = 0.020). Altogether, there was no systematic change of TSP due to alcohol.

For CPM, we observed a highly significant effect of "CPM" (F[1,38] = 32.452, P < 0.001, η² = 0.461), indicating overall lower pain ratings in the CPM condition compared with the baseline condition. There were no main effects of "condition" (F[2,76] = 1.222, P = 0.300, η² = 0.031) or "pre-post" (F[1,38] = 0.249, P = 0.621, η² = 0.007). However, there was a significant "CPM" × "pre-post" interaction (F[1,38] = 8.999, P = 0.005, η² = 0.190), with pain ratings descriptively increasing from T1 to T2 in the baseline condition but decreasing in the CPM condition (Table 2), suggestive of an inhibitory CPM effect. Most interestingly, we found a "CPM" × "pre-post" × "condition" interaction (F[2,76] = 3.239, P = 0.045, η² = 0.079). Pain ratings in the CPM condition decreased from T1 to T2; however, this decrease was more pronounced in the alcohol conditions compared with the placebo condition. There were no significant "condition" × "pre-post" or "condition" × "CPM" interactions (both P's > 0.170).

To explore the significant three-way interaction, we compared CPM scores between T1 and T2 within each condition (placebo, dose 1, and dose 2) using dependent samples t-tests. Conditioned pain modulation scores increased significantly from T1 to T2 in the alcohol conditions (dose 1: t(23) = 2.312, P = 0.026, d = 0.49; dose 2: t(23) = 3.101, P = 0.004, d = 0.54) but not in the placebo condition (t(23) = 0.663, P = 0.511, d = 0.09) (Fig. 2). It is very noteworthy that both alcohol doses seemed to increase the CPM inhibition, with a greater effect size for dose 2 than for dose 1.

3.4. Alcohol effects on the 2 pain dimensions

The ANOVA yielded a significant main effect of "dimension" (F[1,38] = 51.305, P < 0.001, η² = 0.574), with overall higher ratings for pain intensity than for pain unpleasantness, which is a pattern typically observed for experimental pain.⁴⁹ All other effects failed to pass the level of significance (all P's > 0.05). Most importantly, there was no significant "dimension" × "pre-post" × "condition" interaction (F[2,76] = 0.436, P = 0.648, η² = 0.011). Thus, we did not find any indication that alcohol in the consumed doses acts preferentially on the affective dimension of pain compared with the sensory dimension.

### Table 2

Descriptive statistics (M, SD) of pain measures assessed before (T1) and after (T2) drink administration in each of the 3 drink conditions.

<table>
<thead>
<tr>
<th></th>
<th>Placebo T1</th>
<th>Dose 1 T1</th>
<th>Dose 2 T1</th>
<th>Placebo T2</th>
<th>Dose 1 T2</th>
<th>Dose 2 T2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain threshold (°C)</td>
<td>45.23 (1.58)</td>
<td>45.28 (1.63)</td>
<td>45.42 (1.55)</td>
<td>45.08 (1.58)</td>
<td>45.16 (1.67)</td>
<td>45.68 (1.91)</td>
</tr>
<tr>
<td>Rating singlebase</td>
<td>3.64 (2.15)</td>
<td>3.68 (2.23)</td>
<td>3.21 (1.85)</td>
<td>3.74 (2.35)</td>
<td>3.84 (2.24)</td>
<td>3.67 (2.28)</td>
</tr>
<tr>
<td>Rating seriesbase</td>
<td>4.53 (2.45)</td>
<td>4.85 (2.46)</td>
<td>4.44 (2.33)</td>
<td>4.79 (2.34)</td>
<td>4.81 (2.24)</td>
<td>4.68 (2.38)</td>
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<tr>
<td><strong>CPM</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Rating singleCPM</td>
<td>3.07 (2.17)</td>
<td>3.20 (2.14)</td>
<td>3.05 (2.26)</td>
<td>3.09 (2.17)</td>
<td>2.91 (2.17)</td>
<td>2.91 (2.27)</td>
</tr>
<tr>
<td>Rating CS</td>
<td>5.51 (2.32)</td>
<td>5.62 (2.55)</td>
<td>5.48 (2.39)</td>
<td>5.44 (2.46)</td>
<td>6.09 (2.38)</td>
<td>6.05 (2.52)</td>
</tr>
</tbody>
</table>

CPM: conditioned pain modulation; CS: conditioning stimulus; M, mean; TSP: temporal summation of pain.
3.5. Conditioning stimulus ratings: alcohol effects and correlations with conditioned pain modulation

For CS ratings, the ANOVA yielded a significant main effect of "pre-post" (F(1, 38) = 5.937, P = 0.020, η² = 0.135), which was presumably based on an increase from T1 to T2 in both alcohol conditions (Table 2). Confirming this assumption, there was also a significant "pre-post" × "condition" interaction (F(2, 76) = 5.901, P = 0.004, η² = 0.134), with significant increases in the alcohol conditions (dose 1: t(38) = 2.113, P = 0.041, d = 0.19; dose 2: t(38) = 3.361, P = 0.002, d = 0.23) but no significant change in the placebo condition (t(38) = 0.584, P = 0.563, d = 0.03). Thus, we found evidence for hyperalgesic changes in response to tonic hot-water immersion after alcohol intake.

However, there were no significant correlations between CS ratings and CPM scores within each condition (r’s ranging from -0.226 to 0.299; all P’s > 0.050, Bonferroni-corrected α = 0.008). In addition, pre-post changes (T2 - T1) in CS ratings were not correlated with pre-post changes in CPM scores within each condition (placebo: r = 0.139, P = 0.397; dose 1: r = 0.249, P = 0.127; and dose 2: r = 0.011, P = 0.949). Thus, although CS ratings increased after alcohol, the changes in CPM were widely independent from them.

3.6. Alcohol effects on mood

The ANOVA yielded a significant main effect of "pre-post" (F(1, 38) = 4.859, P = 0.034, η² = 0.113), with overall lower POMS scores at T3 compared to T2, indicating an improvement in mood after drink administration. However, we also detected a significant "pre-post" × "condition" interaction (F(2, 76) = 4.332, P = 0.017, η² = 0.102). Post hoc tests revealed that this decrease was significant only in the placebo condition (t(38) = 3.317, P = 0.002, d = 0.50) but not in the dose 1 (t(38) = 0.159, P = 0.875, d = 0.02) or the dose 2 condition (t(38) = 1.197, P = 0.239, d = 0.13).

Taken together, an improvement in mood after drink administration was observed only in the placebo condition but not in the alcohol conditions. Thus, we found no support for mood-enhancing effects of alcohol in our experimental design.

4. Discussion

To the best of our knowledge, our study was the first to investigate alcohol effects on endogenous pain modulation (TSP and CPM). The most remarkable finding was an enhancement of CPM after alcohol intake, which was evident for both doses but more pronounced for the higher dose. In contrast, we found no indication for alcohol effects on TSP. In line with previous studies, weak analgesic effects on pain threshold were observed. The implications of these findings will be discussed in the following paragraphs.

It is notable that the moderate alcohol doses applied in our study boosted endogenous pain inhibition (CPM) in pain-free social drinkers. Although our experimental design does not allow for conclusions regarding the involved mechanisms, some indications can be inferred from previous research. Alcohol triggers the release of endogenous opioids, and this might in turn boost CPM as indicated by several studies reporting CPM being blocked by naloxone/naltrexone or enhanced by opioid medication in healthy subjects and chronic pain patients. In addition, alcohol increases serotonin release, and DNIC studies in animals suggest an involvement of serotonergic and noradrenergic mechanisms in CPM. In line with this, the analgesic acetaminophen, which acts through serotonergic pathways in the spinal cord, was effective in enhancing CPM in healthy control and chronic pain patients, and the selective serotonin-norepinephrine reuptake inhibitor duloxetine was found to restore CPM in patients with diabetic polyneuropathy. Apart from these neurotransmitter mechanisms, the unexpected hyperalgesic effects of alcohol regarding hot-water immersion, which served as CS, might have also contributed to CPM enhancement because a few studies found an association between perceived CS intensity and size of the CPM effect. However, although both CPM magnitude and CS ratings increased after alcohol, all correlations failed significance, thus rather corroborating studies reporting CPM to be independent of the conditioning pain intensity. There might be several explanations for the paradox increase in CS ratings after alcohol. One might be the narrowing of attention to the most salient stimuli which often occurs under the influence of alcohol ("alcohol myopia"); enhanced attention to the hot water bath after alcohol consumption might have led to an increase in pain ratings. Alternatively, alcohol-driven alterations in thermoregulation might be responsible for this effect. It has been shown that even low doses of alcohol increase whole-body heat sensation in a heated room through a decrease in deep-body temperature. It seems conceivable that this enhanced heat sensitivity might also affect the perception of heat stimuli. This effect might become obvious only for stimuli with a certain duration and spatial extension—like hot water immersion of the hand for several minutes—while not affecting the perception of brief stimuli applied to a small area—like our contact heat pulses. Future research is needed to clarify the effects of alcohol on the perception of innocuous and noxious heat stimuli with different perceptual qualities (eg., phasic vs tonic stimulation).

Interestingly, TSP—which captures the excitatory side of pain modulation—remained unchanged after alcohol intake. This is somewhat surprising, given that TSP is driven by NMDA receptor activity and alcohol is known to act as a potent NMDA receptor inhibitor. However, the moderate alcohol doses used in our study might have been too low to induce noticeable effects on NMDA functioning. Previous findings suggest that GABAergic effects of alcohol prevail at lower alcohol doses, whereas effects on NMDA function are most relevant at intoxicating levels. It might be of interest to directly compare the effects of different alcohol doses on TSP to the effects of other NMDA inhibitors (ketamine and dextromethorphan), which have already proven to inhibit TSP in experimental studies.
Alcohol effects on pain threshold, which was included as a traditional measure of static pain perception, were weak and obvious only for the higher dose. This is in accordance with the dose dependency of alcohol effects on pain threshold reported in the recent meta-analysis⁶⁰ and the fact that BrACs ≤ 0.06% produced inconsistent findings regarding effects on pain threshold in previous studies.⁵,⁴⁶,⁵²

Regarding effects of alcohol on the 2 pain dimensions, we found no evidence for a preferential modulation of the affective dimension, thus contrasting 2 previous studies reporting more pronounced effects on unpleasantness than intensity ratings.²²,⁵⁸ In line with this, we also observed no improvement in mood after alcohol intake, which might be due to the experimental situation involving very little social contact and rather unpleasant procedures. Besides the pain stimulation being stressful, the taste of the drink (both the placebo and the alcoholic version) was not very pleasant as reported by several participants and the short time allowed for drink consumption was rather challenging. In this context, unpleasant alcohol effects such as dizziness might have prevailed over mood-enhancing effects. Thus, our findings suggest that the pain reduction after alcohol consumption observed in our study likely resulted from true analgesic properties of alcohol rather than from its emotionally modulating properties. However, this does not rule out the possibility that emotional effects might be implicated in pain-dampening effects of alcohol in a more naturalistic setting.

4.1. Strengths and limitations

The main strength of our study was the combination of a naturalistic alcohol application (subtoxic doses and oral ingestion) with an experimental design complying with common standards for the study of pharmacological effects (placebo control, double blinding, and randomization).²⁹

One potential limitation could be seen in the fact that BrACs did not reach the targeted levels, although we tried our best to individually titrate the alcohol doses using a two-step procedure. Thus, alcohol levels might have been too low to exert effects on some measures, particularly on TSP. In addition, our study was the first to investigate alcohol effects on pain elicited by contact heat, which could be seen as a limitation due to limited comparability with previous research using other stimulus modalities. However, this modality was intentionally chosen because it provides a nociceptive-specific,⁵¹ natural noxious stimulation (unlike electrical stimuli) and does not produce unwanted side effects (unlike the CPT that triggers intense cardiovascular stress).²⁴ In addition, it is frequently used in psychophysiological investigations⁵⁷ as well as pharmacological pain research,⁵⁶ and the combination of contact heat as TS and hot water as CS has been established as the standard CPM paradigm in our laboratory, which made it ideally suited for testing for the first time alcohol effects on CPM. Although stimulus modality was not found to be a moderator of alcohol effects in the recent meta-analysis,⁶⁰ testing TSP and CPM derived from other stimulus modalities (eg, pressure) should be the logical next step in future research. Furthermore, the inclusion of electrophysiological measurements (EEG and evoked potentials) might add information about general and nociceptive-specific central arousal and the occurrence and interaction of alcohol-dependent and pain-related physiological changes in alcohol effects on pain. However, because our study was, to the best of our knowledge, the first examination of alcohol effects on endogenous pain modulation, we straightforwardly focused for this time on subjective pain parameters as the traditional measures to assess TSP and CPM.

5. Conclusions

Our study provided evidence for an enhancement of CPM by moderate alcohol doses, whereas no effects on TSP were observed. Thus, analgesic effects of alcohol might be driven rather by boosting endogenous pain inhibition than by blocking excitatory mechanisms. This might have important clinical implications because deficient CPM has been reported for many idiopathic pain syndromes⁶⁵ and could also be associated with an increased use of analgesics after surgery.²⁹ The successful enhancement of endogenous pain inhibition by alcohol—as shown in this study—might become a risky incentive for using alcohol as self-treatment of pain; dose enhancement—as kind of tolerance development—might soon become necessary to maintain sufficient analgesia. This might also explain the frequent occurrence of alcohol misuse in pain samples.¹³,²⁰,³⁸,⁵³ Thus, deficient CPM might be a risk factor for developing alcohol use disorders in individuals with an increased vulnerability for pain. Based on these considerations, a next step will be to test the effects of alcohol on CPM and TSP in individuals suffering from chronic pain.

Conflict of interest statement

The authors have no conflict of interest to declare.

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