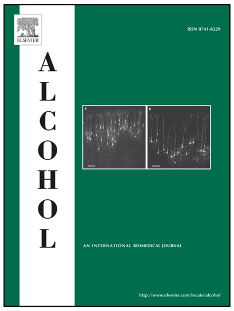
Journal Pre-proof



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PII: S0741-8329(24)00177-0

DOI: https://doi.org/10.1016/j.alcohol.2024.11.004

Reference: ALC 7337

To appear in: *Alcohol*

Received Date: 26 July 2024

Revised Date: 26 October 2024

Accepted Date: 21 November 2024

Please cite this article as: Harkki J., Tuovinen P., Jousimäki V., Barreto G., Rapeli P., Palomäki J., Annevirta J., Puisto A.-H., McGlone F., Nieminen H. & Alho H., CT-optimal touch modulates alcohol-cue-elicited heart rate variability in Alcohol Use Disorder patients during early abstinence: a randomized controlled study *Alcohol*, https://doi.org/10.1016/j.alcohol.2024.11.004.

CT-optimal touch modulates alcohol-cue-elicited heart rate variability in Alcohol Use Disorder patients during early abstinence: a randomized controlled study

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Declaration of interest: JH and PT hold a patent for a mechanism for a CT-optimal haptic device (IPID3248). Other authors have no interests to declear.

Abstract

Alcohol Use Disorder (AUD) is a chronic brain disorder associated with a high risk of relapse and a limited treatment efficacy. Relapses may occur even after long periods of abstinence and are often triggered by stress or cue induced alcohol craving. C-tactile afferents (CT) are cutaneous nerve fibers postulated to encode pleasant affective touch and known to modulate physiological stress responses. However, their translational potential has not yet been explored extensively in controlled clinical trials. This randomized controlled study aimed to investigate the potential of CT stimulation in modulating relapse predicting biomarkers, physiological cue-reactivity, and subjective alcohol craving in AUD patients in early abstinence.

Twenty-one participants meeting DSM-5 criteria for mild to moderate AUD received CT-optimal touch or a non-CT-optimal control treatment while exposed to neutral, stress-inducing, and alcohol-related visual stimuli. The tactile treatment was provided with a robotic device, eliminating the social elements of touch. Heart rate variability (HRV), salivary cortisol, and subjective craving were assessed at the baseline, during and after the treatment and stimuli exposure.

The results showed that CT-optimal touch significantly reduced alcohol-cue-elicited standard deviation of normal-to-normal intervals (SDNN) HRV compared to the control group, shifting the HRV reactivity to the direction known to indicate lower relapse susceptibility. Cortisol levels showed no significant differences between the groups, and subjective alcohol craving increased after alcohol cue exposure in both groups.

This study found that CT-optimal touch modulates autonomic cue-reactivity in AUD patients, encouraging further research on the therapeutic potential of affective touch. Future research should explore the long-term effects and real-world clinical relevance of CT-optimal touch in alcohol relapse prevention.

Keywords: Affective touch, Alcohol Use Disorder, C-tactile afferents, cue-reactivity, craving, heart rate variability, stress, randomized controlled trial.

Introduction

Alcohol use disorder (AUD) is a chronic brain disorder with a high risk of relapse even after long periods of abstinence. Eventual relapse occurs in up to 75% of the patients attempting to quit drinking with current pharmacological and psychosocial treatments (Boothby & Doering, 2005). The high relapse rate indicates the critical need for novel interventions. However, few relapse-preventing therapies have emerged since the approval of opioid receptor antagonists, such as naltrexone, nearly 30 years ago (Center for Substance Abuse Treatment, 2009).

One of the characteristic symptoms of AUD and an important contributor to relapses is alcohol craving (Koob & Volkow, 2016; Sinha, 2013b). Craving may be triggered by alcohol-related cues, i.e. incentive saliences that precipitate the abnormally high dopaminergic activity in the nucleus accumbens (NAc) associated with the hedonic state of alcohol intake. Another equally important trigger for craving is negative mental stress, involving the hypothalamic pituitary adrenal (HPA) axis, amygdala and peripheral stress responses (Koob, 2013; Koob & Volkow, 2016; Sinha, 2013b). Exposure to chronic stressors or aversive life events is known to increase the risk of harmful use of alcohol and the severity of AUD (Sinha, 2022). Moreover, aversive stress-related symptoms, such as anxiety, negative mood and aggressive behaviour, are typical in early abstinence from alcohol, which may further increase craving and the risk of a relapse (Koob & Volkow, 2016; Sinha, 2013a). In short, stress has a bidirectional impact on alcohol craving and the occurrence of relapses; it may trigger craving, leading to the harmful use of alcohol, whereas the harmful use of alcohol may generate the symptoms of stress contributing to the vicious cycle of addiction.

Neural adaptations resulting from a chronic use of alcohol alter both peripheral and central stress systems, manifesting, for instance, as dysregulation of the autonomic nervous system (ANS) (Blaine et al., 2017; Koob, 2013; Sinha, 2009; Sinha et al., 2009). This neural dysregulation is illustrated clearly by heart rate variability (HRV), an established biomarker of ANS activity. Generally, in a healthy population, a higher resting state HRV is considered to reflect higher activity of the parasympathetic division of ANS, thus indicating a lower stress level. Correspondingly, stress exposure typically leads to a decrease in HRV. However, numerous studies have shown that AUD patients have an abnormally low resting state HRV, yet it increases when exposed to stressors or alcohol-cues (for reviews see Cheng et al., 2019; Ralevski et al., 2019). Furthermore, heightened high-frequency HRV in response to alcohol-cues predicts susceptibility to relapse in abstinent AUD patients, suggesting that HRV may be used as a relapse predicting biomarker (Garland et al., 2012).

As stress has been recognized as one of the key factors in alcohol craving and relapses, treatments targeting stress-related mechanisms have attracted research interest in recent years. However, to the best of our knowledge, no previous studies in this field have addressed the potential stress regulating properties of somatosensory systems, namely C-tactile afferents (CT).

CTs are slowly conducting unmyelinated low-threshold mechanoreceptor nerve fibers that are postulated to code for the pleasant (rewarding) properties of social and affective touch (Löken et al., 2009; McGlone et al., 2014; Olausson et al., 2016; Pawling et al., 2017). The optimal range of tactile stimulus velocity for CT firing is from 1 to 10 cm / s; both slower and faster speeds resulting in a weaker response in the firing rate of CTs during microneurography experiments (Löken et al., 2009). This velocity is also typical for gentle social touch, such as a caress. For instance, Püschel et al (2022) showed that mothers who were asked to stroke their preterm infants, did so in the CT-optimal velocity range. Further microneurography studies have shown that the firing frequency of CTs positively correlates with perceived pleasantness of skin stroking (Essick et al., 1999; Essick et al., 2010; Löken et al., 2009). These observations are supported by a study by Morrison et al. (2011), which showed that patients with a genetic deficit of C-fibers rated CT optimal skin stroking as less pleasant than did the control group of healthy individuals.

CTs interact with several neurobiological mechanisms associated with AUD. Firstly, they project to the insular cortex (IC), a region of high importance in interoception and affective processes, also known to be a crucial brain site in modulation of cue-induced substance craving (Björnsdotter et al., 2009; Davidovic et al., 2019; Löken et al., 2009; Naqvi et al., 2014; H. Olausson et al., 2002; Olausson et al., 2016; Pawling et al., 2017). The IC has functional connectivity with brain regions central to reward, motivation, and addictive processes, influencing dopaminergic activity within the ventral tegmental area and NAc (Girven et al., 2020). The elevated dopamine levels in the NAc also occur as a result of tactile skin stimulation, further highlighting the effect of affective touch on reward pathways (Maruyama et al., 2012). Moreover, affective social touch, typically applied at CT-optimal velocity and force, modulates the endogenous μ-opioid system, known to have a pivotal role in alcohol-induced dopamine increase and the pleasurable effects of alcohol (Gilpin & Koob, 2008; Korpi et al., 2015; Nummenmaa et al., 2016).

Crucially, CT-optimal touch seems to effectively modulate stress responses. Hence the affective touch system has been suggested as an indispensable component of our physiological stress regulation (Morrison, 2016; Blaine et al., 2017; Pawling et al., 2017b). One of the most intriguing examples of this is a study by Walker et al (2020), which demonstrated that a mere 10 minutes of slow stroking touch per day had a striking effect on stress-resilience in rats, nearly abolishing the anxiety-related behaviour and corticosterone increase in a rodent model of chronic mild stress. Human studies have shown that CT-optimal and affective touch have an ability to both increase oxytocin and to lower cortisol level, as well as to reduce peripheral stress system activity manifesting, for instance, as a lower heart rate (Ditzen et al., 2007; Eckstein et al., 2020; King & Becker, 2019; Püschel et al., 2022; Uvnäs-Moberg et al., 2014; Walker et al., 2017). Importantly, CT-optimal touch has been identified as a potent modulator of HRV. For instance, a study by Triscoli et al. (2017) showed that HRV of healthy subjects increases with robotic CT-optimal stroking touch. Moreover, a recent study demonstrated that dynamic touch at CT-optimal velocity, increased the HRV of preterm infants, whereas static touch had no such effect (Manzotti et al., 2023). However, to date, no published data exists on the potential effects of CT-optimal touch on HRV and ANS regulation in the AUD patient population.

Building on this foundation, we hypothesize that the rewarding and stress-regulating effects of CT-optimal touch may influence physiological cue-reactivity, subsequently reducing alcohol craving and preventing relapses. To test this, we investigated the impact of acute CT-optimal touch on HRV reactivity, salivary cortisol, and self-reported craving of early abstinent AUD patients in stress- and alcohol-cue exposure. Comparable protocols have previously been used in drug research (e.g. Fox et al., 2012), however, instead of pharmacological intervention, in this body of work, we explored the effect of CT-optimal tactile stimulation.

Materials and methods

Experimental design

This study was a randomized single-blinded controlled trial with two parallel treatment groups (CT-optimal treatment and non-CT-optimal control treatment). The study was conducted in accordance with the Declaration of Helsinki and European Union's General Data Protection Regulation. The research plan was pre-evaluated and approved by the Helsinki University Hospital Regional Committee on Medical Research Ethics (HUS/11938/2022).

Participants

Twenty-one participants (10 female) of ages 27 to 60 (mean 48) took part in the study. The participants were randomly assigned to active treatment (CT-optimal touch, n=11) and control treatment (non-CT-optimal touch, n=10) groups. All participants met the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for mild to moderate Alcohol Use Disorder (AUD) and had maintained a minimum of 14 days without engaging in heavy alcohol consumption. Heavy alcohol consumption was defined as ≥ 60 g of absolute alcohol per day for males and ≥ 40 g per day for females. The participants were recruited via social media.

The participants were instructed to avoid caffeinated drinks for 24 hours, physical exercise for 3 hours and eating, drinking and smoking for 1 hour before the experiment. On attending the test facility, the participants signed the informed consent and were familiarized with the protocol. A breathalyser test was performed to confirm the breath alcohol concentration was at the undetectable level and absence of withdrawal symptoms was ensured with Clinical Institute Withdrawal assessment for Alcohol questioner (Ciwa-ar) (Sullivan et al., 1989). The heavy drinking days of the past 6 weeks were recorded in the Timeline Follow Back Calendar (TLFB) (Sobell & Sobell, 1990) and Obsessive Compulsive Drinking Scale (OCDS) (Anton et al., 1996) was used to assess the overall recent alcohol craving (mean total score 18.05)

The exclusion criteria included diagnosis of concomitant psychiatric disorders, current use of addictive substances other than alcohol (excluding nicotine), mood-regulating medications, recent participation in a treatment program for alcohol use disorders, autism spectrum disorder (score ≥ 26 in Autism-Spectrum Quotient test, (Baron-Cohen et al., 2001)), dermatological conditions and cardiovascular or other clinically relevant unstable or untreated illnesses.

Treatments

To eliminate the social aspect present in human touch, we used a robotic device to provide the CT-optimal dynamic touch. Both CT-optimal touch treatment and the non-CT-optimal control treatment were performed with the same robotic device that provided dynamic back- and forth strokes with a soft cosmetic brush on the skin of the left (non-dominant) forearm of the participants. The CT-optimal treatment was performed at a velocity of 2.5 to 3 cm/s and a force of 200 to 300 mN. The non-CT-optimal control treatment was performed with velocity of 0.1 to 0.2 cm/s and a force similar to the CT-optimal treatment. The device was visible to the participants during the experiment.

The custom-made robot used for producing the haptic stimulation was designed in a similar way as in the study by Eriksson Hagberg *et al* (2019) in which a similar stimulator was used to study activation of skin nerve fibers and related brain activity. Two pneumatic muscles were used to ensure the controlled distance, force, and velocity. The pneumatic muscles were operated with compressed air that was adjusted with a pneumatic control system located at a safe distance from the participant. The muscles were reinforced and supported with glass-fiber composite tubes and plastic polypropylene connectors. The stimulator was equipped with an optoswitch to measure the velocity of the brush, and a load cell to measure the applied force on the skin and to identify the skin contact. A photograph of the robot is shown in Supplement 1.

Stimuli

To expose participants to triggers known to induce alcohol craving, the subjects were presented with alcohol-related and stress-inducing images. Neutral images that typically do not induce craving, were shown as a control condition. The images for the neutral and stress stimuli were chosen from International Affective Picture System database (IAPS)(Lang, P.J. Bradley, M.M., & Cuthbert, 2008). Each set of images contained 30 pictures of one type of stimulus, each image being visible for 10 s. The images were presented on a 27 inch monitor (ThinkVision E27q-20, Lenovo, Quarry Bay, Hong Kong) located approximately 60 cm away from the participant. All participants were exposed to all three types of stimuli on separate consecutive sessions in the following order: neutral, stress-inducing, alcohol-related. The mean valence/arousal ratings for the selected neutral IAPS images were 6.4/3.3 and the images contained, for instance, landscapes and details of nature. The mean valence/arousal ratings for the selected stress-inducing images were 2.3/6.3 (range 1 to 9) and the images included, for instance, violence, mutilated or severely damaged human bodies and attacking animals. The alcohol-related images were chosen from The Geneva Appetitive Alcohol Picture database (GAAP) (Billieux et al., 2011), which contain images of alcoholic drinks, bars, night clubs, and people drinking. The alcohol-related visual material was adapted to suit the participant's personal preference by ensuring that the material contains images of their preferred type of alcoholic beverage. In addition, the material was modified to be recognisable for the Finnish AUD patients, for example by replacing an image of a Swiss beer bottle with a Finnish equivalent sourced from the internet.

HRV reactivity

To assess autonomic functioning, HRV was derived from blood volume pulse (BVP) measured with Empatica E4 wrist band device (Empatica Inc., Milan, Italy) throughout each session excluding a 15-minute relaxation at the end of the session (Fig. 1). Of many HRV parameters, standard deviation of normal-to-normal intervals (SDNN) was selected, as CT-optimal touch has been previously show to modulate SDNN (Triscoli et al., 2017). Kubios HRV Scientific software (Kubios Oy, Kuopio, Finland) was used to analyse HRV from the BVP data using automatic artefact correction. We analysed the mean SDNN HRV of four 5-minute blocks from the following time points of each session: baseline, treatment minutes 5 to 10, visual stimulation, treatment minutes 20 to 25 (recovery). To determine the HRV reactivity of each participant, the change of the SDNN HRV was calculated for each session by subtracting the baseline value from the stimulation value and for the whole experiment by subtracting the baseline value of the first session from the values of each time point of the whole experiment.

Subjective alcohol craving

To assess the subjective alcohol craving, we asked the participants to rate their current craving on a 10-point horizontal visual analogue scale (VAS). The rating was performed at three timepoints per session; the baseline, after the visual stimuli and at the end of the treatment (Fig. 1.). The lowest value (point 1) on the VAS equalled the statement "*If alcohol was now available, I would not want to drink it at all"*, whereas the highest value (the point 10) equalled the statement "*If alcohol was now available, I would not be able to resist drinking even if I tried".* The VAS was presented to the participant on the same screen as the visual stimuli and the participant gave the rating by saying aloud the number corresponding the current state of their subjective alcohol craving.

Salivary cortisol level

To assess the salivary cortisol levels, saliva samples were collected 5 times during each session (total 15 samples per participant) (Fig. 1.). The time points of the saliva collection were the baseline, after the first 10 minutes of the treatment, after the visual stimuli, at the end of the treatment and after the 15-minute relaxation period. The saliva was collected by placing a synthetic swab (Salivette Cortisol, Sarstedt Inc. Nümbrecht, Germany) between the tongue and the cheek of the participants for minimum 2 minutes after which it was placed in a plastic tube (Salivette) and stored in -20 °C until the analysis. Once the samples were thawed, they were centrifuged in 1000 x g for 2 minutes. The samples were analysed with a competitive enzyme-linked immunosorbent assay (Cortisol free in Saliva ELISA DES6611, Demeditec Diagnostics GmbH, Kiel, Germany) and the optical density was determined at 450 nm with a well-plate reader (FLUOstar Omega, BMG Labtech, Ortenberg, Germany). If the sample had less than 50 µl of saliva it was diluted to 1:2 or 1:5 ratio with Calibrator 0. The concentrations were interpolated from the absorbance values with GraphPad Prism v. 10.1.1 software (GraphPad Software LLC, Boston, United States) using 4PL curve fit.

Procedure

The experiment included three consecutive sessions in which the participants were exposed to neutral, stress-inducing and alcohol-cue images with one type of stimuli per session while they received either the CT-optimal or the control treatment. The structure of one session is illustrated in Fig. 1.

At the start of each session, the participants were instructed to sit still in a comfortable position avoiding any movement. To block the noise from the pneumatic device participants were asked to wear earplugs. Each session started with a saliva sample and a VAS rating followed by the baseline BVP measurement. After this, the treatment was started and continued for 25 minutes including the 5-minute visual stimuli prestation in the middle. The treatment was followed by a 15-minute relaxation during which the participant was allowed to stand up, walk and move lightly. Total length of one session was approximately 47 minutes.

** Fig 1. **

After the three sessions participants had a chance to participate in a voice-guided relaxation session to ensure the absence of a possible craving or stress triggered by the experiment. In addition, all participants were offered a consultation of an addiction specialist physician after their participation.

The study included a second visit that contained a cue-reactivity task test with pupillary reactivity and EEG measurements. The second experiment was followed by a two-week follow-up period during which the participants were asked to report the daily subjective craving, alcohol consumption and possible adverse events by filling an online diary. The results of the second experiment, as well as the follow-up, will be reported in separate publications.

Statistical analysis

Statistical analysis was performed with GraphPad Prism v. 10.1.1 software (GraphPad Software LLC, Boston, United States) software. Normality of the HRV reactivity data of each session was confirmed and the data was analysed with an unpaired t-test. The change of the mean HRV, the mean VAS craving ratings and the mean cortisol levels from the initial baseline throughout the whole experiment (all three sessions and all time points) were analysed independently with a repeated measures two-way analysis of variance (ANOVA). A multiple linear regression analysis was conducted with HRV reactivity of the alcohol-cue session as the dependent variable and treatment, initial baseline HRV, number of heavy drinking days in TLFB, OCDS score, the mean change of the craving ratings in VAS in alcohol-cue session and the mean initial baseline craving as independent variables.

Results

HRV reactivity

The HRV of two participants from the CT-optimal treatment group could not be analysed due to the irregular BVP data. Hence, the data of 9 participants from the CT-optimal group and 10 from the control group were included in the analysis. The results of the unpaired t-tests of each sessions mean HRV change from the session's baseline to the stimulation exposure (Fig. 2) showed that the mean SDNN HRV of the CT-optimal treatment group was significantly reduced compared to the control group in alcohol-cue exposure ($R^2 = 0.3$, 95% CI -22.71 to -2.399, $p = 0.0184$). There were no differences in the mean HRV changes between the groups in neutral or stress-inducing stimulation. The individual values are visualized in Supplement 2. The multiple linear regression analysis confirmed that treatment was the only factor having a significant interaction with the alcohol-cue elicited HRV change while neither of other analysed variables (the initial baseline HRV, number of heavy drinking days in TLFB, OCDS score, the mean change of the craving ratings in VAS in alcohol-cue session nor the mean initial baseline craving) were significantly associated with it.

** Fig. 2 **

The mean HRV increased from the initial baseline of the experiment in both treatment groups during the neutral and stress-inducing sessions (Fig. 3). In the control group the increase was seen also during the alcohol-cue session. The results of the repeated measures two-way ANOVA showed that in the control group the chance of the HRV from the baseline was statistically significant ($p < 0.05$) at all analysed time points excluding the baseline measurement of the alcohol-cue session. In the CT-optimal treatment group the HRV was significantly increased from the baseline from the second timepoint of the stress session to the baseline of the alcohol-cue session.

** Fig 3. **

Subjective craving

The mean ratings of subjective alcohol craving were significantly higher after alcohol-cue exposure than after the neutral stimuli exposure in both treatment groups based on the repeated measures two-way ANOVA (CT-optimal group CI 95% -1.964 to -0.2173, p = 0.0194, control group CI 95% -2.469 to -0.5314, p = 0.0067) (Fig. 4). In the CT-optimal treatment group the mean rating after the presentation of alcohol-cues was also significantly higher than the mean craving after the stress stimuli exposure (CI 95% -1.901 to -0.09867, p = 0.0330). However, the stress stimuli did not induce significantly higher craving compared to the neutral stimuli in either group. The statistical analysis of the change of the mean craving ratings from the baseline showed no significant differences between the treatment groups at any timepoint.

** Fig. 4 **

Salivary cortisol level

Of the collected saliva samples 70 had to be discarded due to the insufficient amount of saliva. The data of the analysed samples of 18 participants (8 CT-optimal, 10 controls) were included in the mixed-model analysis which showed no significant differences between the groups in the change of the mean cortisol level. In both groups, the mean cortisol level dropped below the baseline 10 minutes after the stress exposure and remained lower than the baseline until the last measurement of the experiment (Fig. 5). However, this change was statistically significant only for the control group at the timepoint 25 minutes after the stress exposure.

** Fig. **

Discussion

To our knowledge the present study is the first randomized controlled trial investigating the effect of acute CT-optimal touch on cue-reactivity in AUD patients. Based on previous evidence indicating that CT-optimal affective touch can modulate the functioning of the autonomic nervous system and physiological stress responses, we hypothesized that CT-optimal touch may affect the cue-reactivity of abstinent AUD patients. In line with our hypothesis, our results revealed significant differences in HRV reactivity between the CT-optimal touch treatment group and the non-CT-optimal touch control group during alcohol-cue exposure, indicating a modulatory effect of CT-optimal touch on autonomic cue-reactivity. Importantly, this effect was achieved with a robotic device, without the social elements of affective human touch.

Contrary to the HRV patterns observed in healthy individuals, AUD patients typically exhibit a low relaxed state HRV which elevates in response to stress or alcohol-cues. A previous study by Garland et al. (2012) showed that abstinent AUD patients with a lower cue-elicited HRV were significantly less likely to relapse than those with a higher cue-elicited HRV, implying that HRV reactivity may serve as a physiological predictor of a relapse. Building on this foundation, we demonstrated that CT-optimal touch lowers the cue-elicited HRV in AUD patients. Our results suggest that CT activation may shift the HRV reactivity closer to that of a healthy social drinker or an AUD patient with a lower susceptibility to relapse. However, these results require to be replicated in a larger patient group and the possible clinical relevance must be evaluated outside the laboratory to investigate whether the physiological modulation translates into a reduction in relapses.

Alongside the altered HRV, the AUD-related dysregulation of physiological stress responses manifests as a high baseline cortisol level that decreases in response to stress or cue exposure (Junghanns et al., 2005; Sinha, 2013a). Although we observed a reduction in cortisol concentrations after stress exposure in both groups, CT-optimal touch did not exert a notable effect on cortisol concentrations under any condition. This finding is consistent with the study by Triscoli et al. (2017), which demonstrated that CT-optimal robotic touch modulated HRV but not salivary cortisol levels in healthy subjects.

Throughout the experiment, alcohol craving remained moderately low in both groups, although it significantly increased after exposure to alcohol cues. Environmental factors, such as the laboratory setting and the time of day, may have influenced these results. The type of treatment did not influence the subjective experience of alcohol craving which increased equally in both groups after the cue exposure. In addition, the differences in HRV reactivity between the groups did not relate to the craving ratings. These results align with prior observations suggesting that physiological responses to alcohol-cues do not consistently correlate with conscious craving (Heinz et al., 2010). Importantly, physiological responses have been identified as more reliable predictors of relapse and addiction-related behavior than conscious substance craving (Heinz et al., 2010).

In contrast to our hypothesis, no significant differences in HRV reactivity were observed between groups during the stress exposure. Additionally, neither group exhibited an increase in craving ratings in response to stress stimuli, suggesting that the chosen stimulation material failed to induce the intended psychosocial stress in this patient group, although similar visual stimuli have been successfully used in studies with AUD patients before (Garland et al., 2012).

Several limitations need consideration regarding this study. Firstly, our sample size was smaller than initially intended due to challenges in recruiting patients who both met the inclusion criteria and attended the scheduled study visit. In the following studies, this challenge could be mitigated by including patients who are already committed to a treatment programme. In future investigations of stress-triggered craving, the type of stress stimuli should be reconsidered, and the stress experience should be assessed using additional tools to enhance the depth of understanding. 22% of the saliva sample were discarded because of insufficient amount of saliva, which may have affected the results of the cortisol reactivity. Future studies may benefit from utilizing serum cortisol instead of salivary cortisol for improved accuracy. Lastly, due to the nature of the intervention and design of the robotic device, double blinding was not possible as the velocity of the skin stroking was visible to the investigators.

In conclusion, our study provides strong preliminary evidence that acute CT-optimal touch modulates HRV reactivity during alcohol-cue exposure in early abstinent AUD patients. The stress-regulating effects of CT-optimal touch make it a promising translational tool and a candidate for potential novel adjunctive therapeutic intervention in the context of AUD. Future research should focus on investigating the long-term outcomes to establish the clinical potential of CT-optimal touch in preventing relapses.

Funding

The study was funded by Business Finland (grant 6622/31/202), Aalto University and The Emil Aaltonen Foundation (grant 230034 N1).

Author contributions

Juliana Harkki: Conseptulization, Metholodology, Formal analysis, Investigation, Writing - original draft, Visualization, Supervision **Pauli Tuovinen:** Conseptulization, Software, Resources, Writing – review & editing **Veikko Jousimäki:** Resources, Writing – review & editing **Goncalo Barretto:** Resources, Writing – review & editing **Pekka Rapeli:** Metholodology, Writing – review & editing **Jussi Palomäki:** Resources, Writing – review & editing **Jonne Annevirta:** Investigation **Anna-Helena Puisto:** Investigation **Francis McGlone:** Conseptulization, Metholodology, Writing – review & editing **Heikki Nieminen:** Conseptulization, Supervision, Writing – review & editing **Hannu Alho:** Conseptulization, Metholodology, Supervision, Writing – review & editing

Acknowledgments

We want to thank Hanna Renvall and Ilkka Nissinen for support, guidance and advice throughout the study, Veli-Matti Saarinen and Helge Kainulainen at Aalto NeuroImaging for their help in setting up the robotic device used in the experiment, Jukka Planman for valuable brainstorming and conversations, Biodesign Finland for planting the seed for this study and the funders for making it possible.

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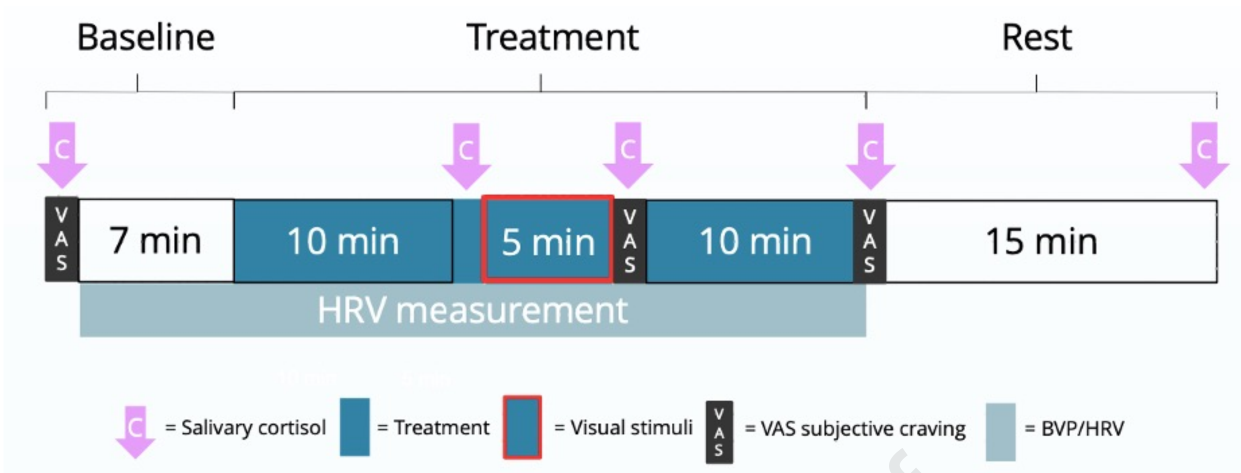

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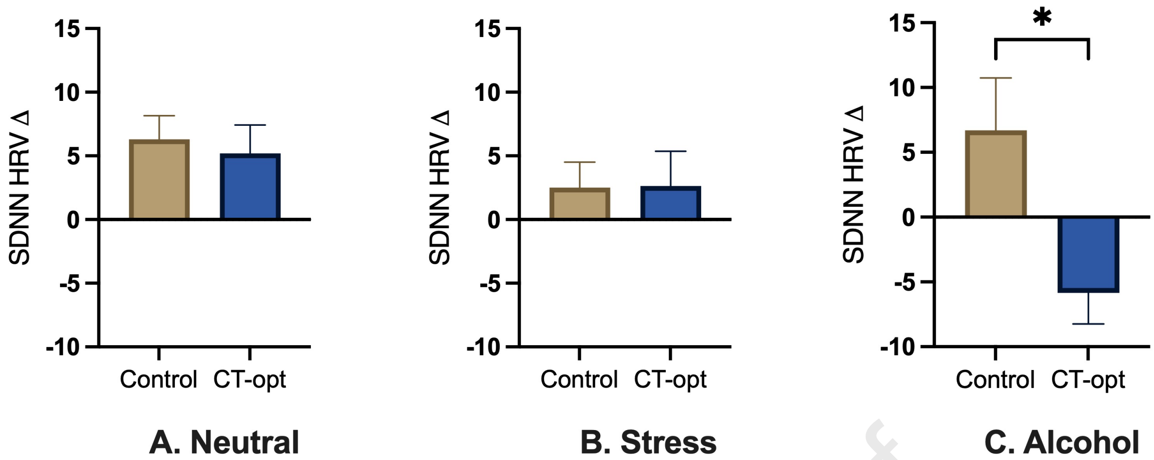
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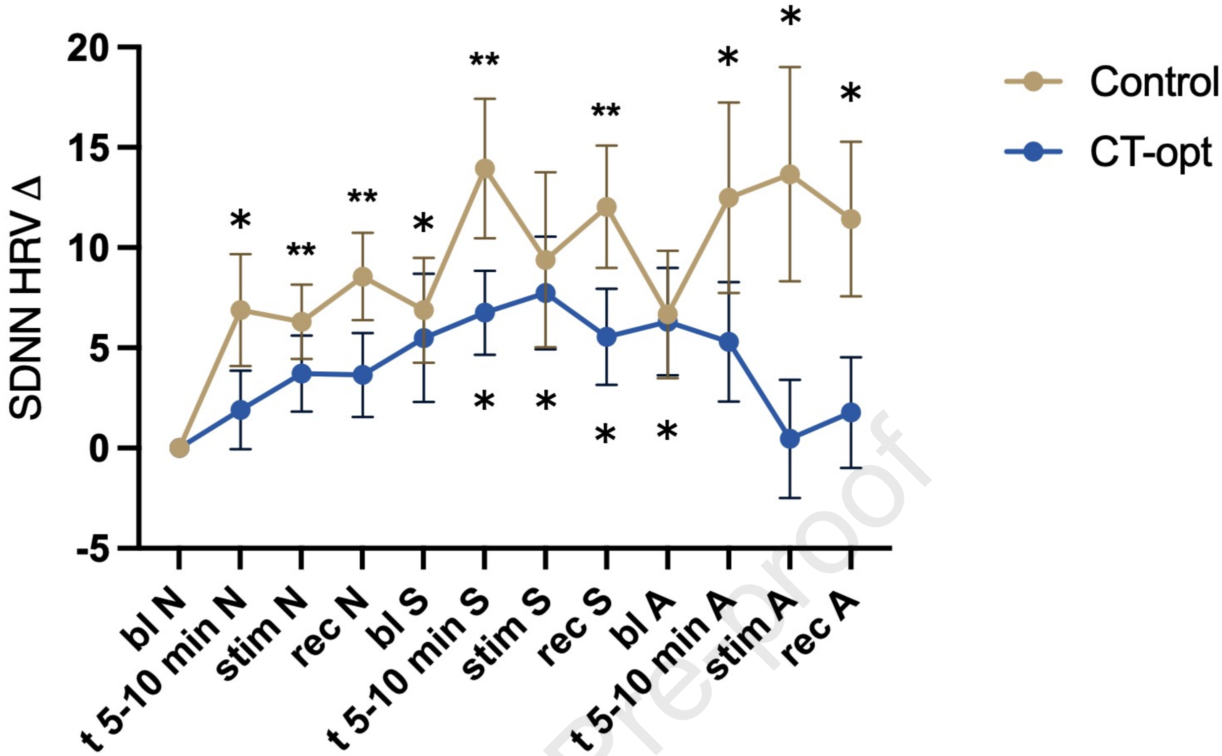
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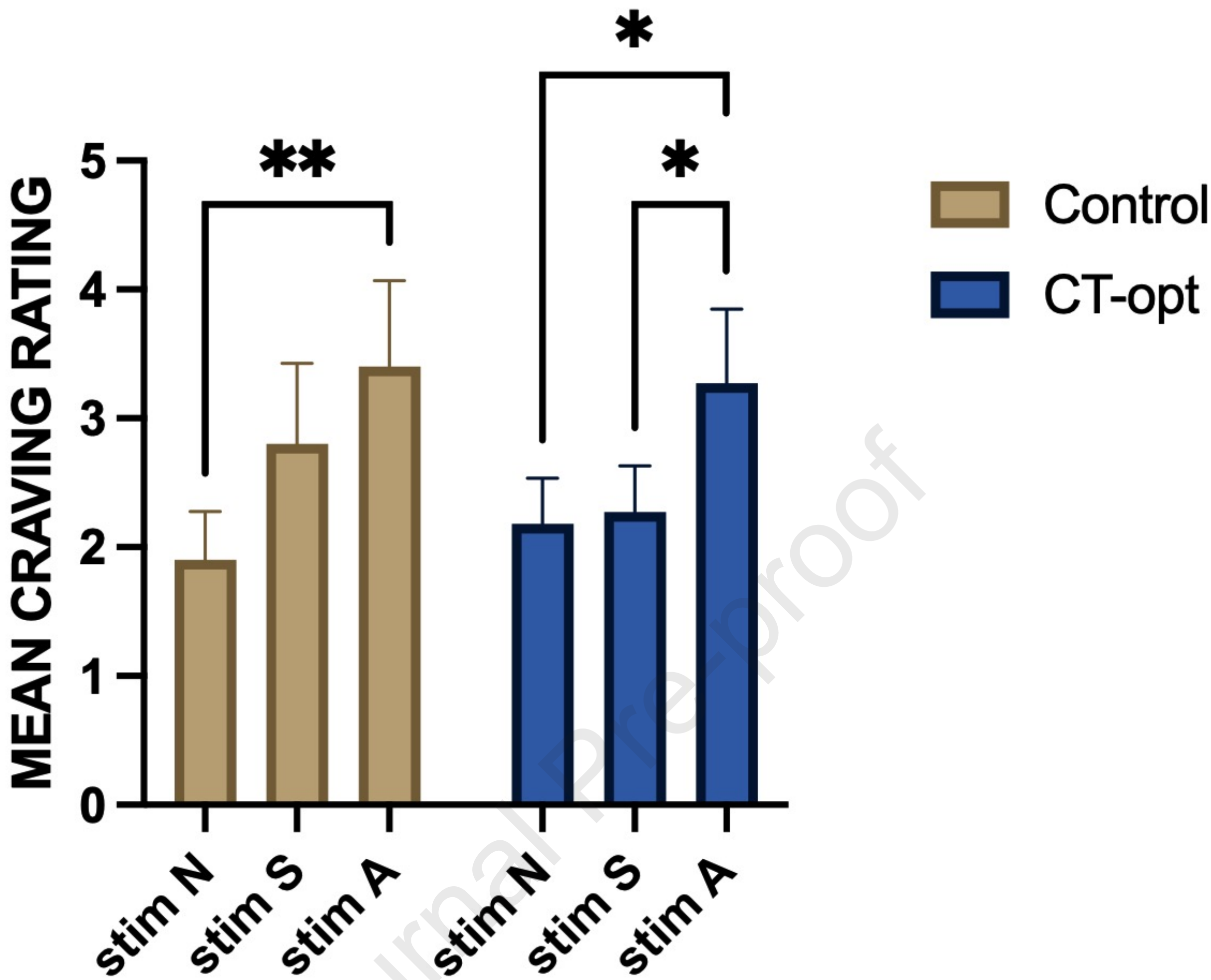

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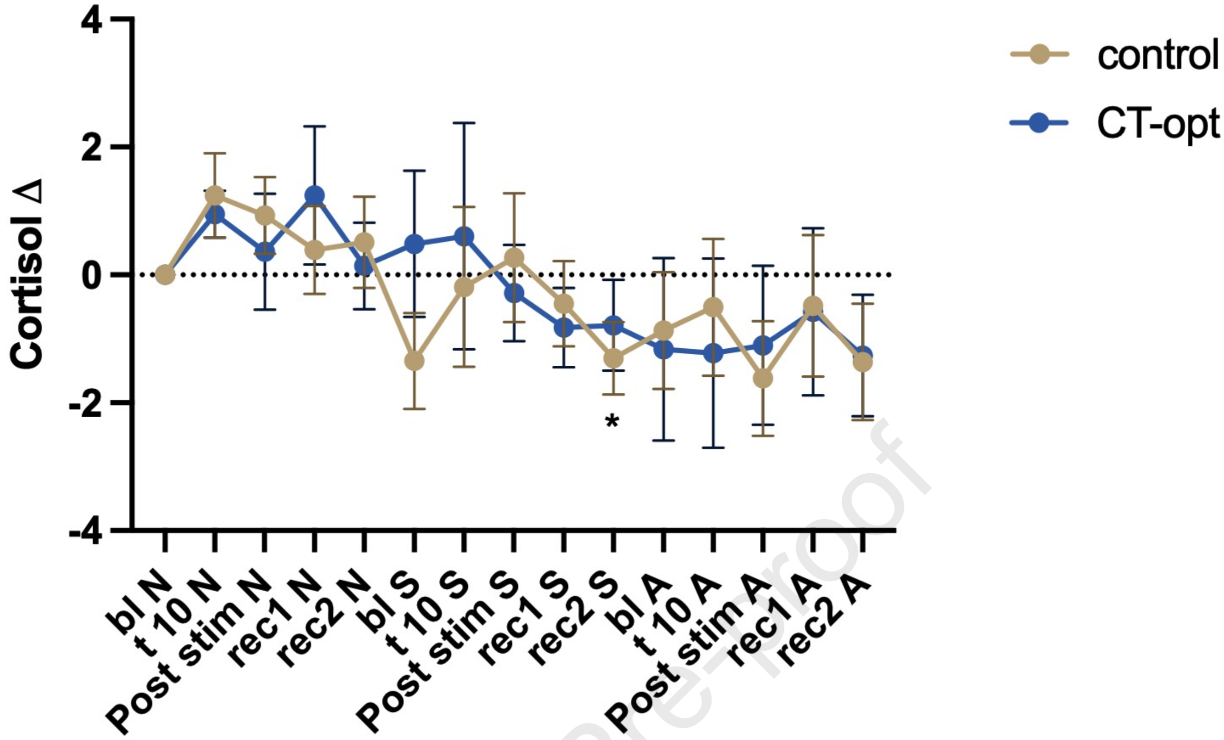
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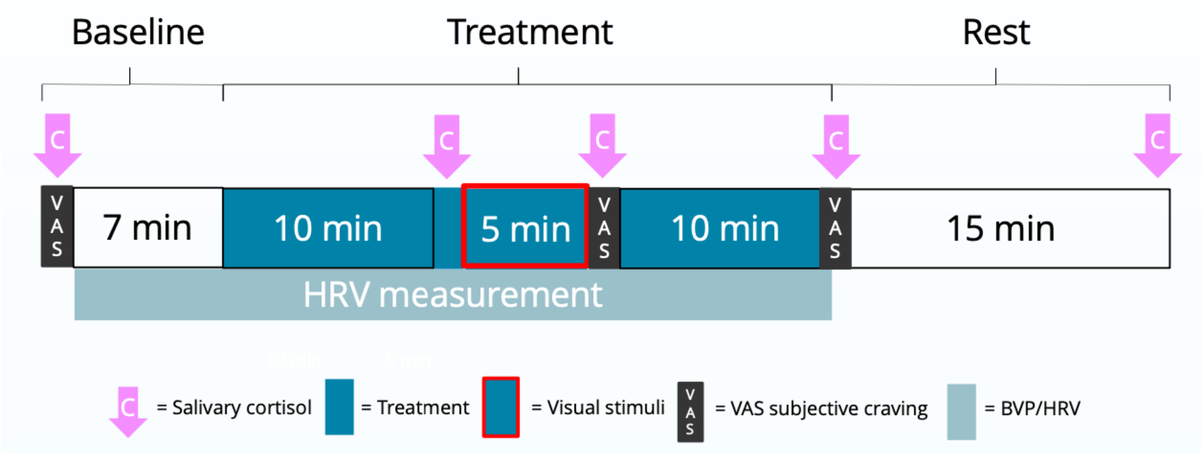

Fig. 1 The design of a single treatment session. The experiment included three consecutive sessions, each with one type of visual stimuli. The subjects were exposed to neutral, stress-inducing or alcohol-related, images, while they received either the CT-optimal or the control treatment. 5 saliva samples were collected during each session. HRV was derived from the BVP that was measured throughout the experiment excluding the 15-minute relaxation in the end of each session. Subjective craving was assessed with VAS at the baseline, after the visual stimuli and after the 25-minute treatment. BVP = Blood volume pulse, HRV = heart rate variability, VAS = visual analog scale.

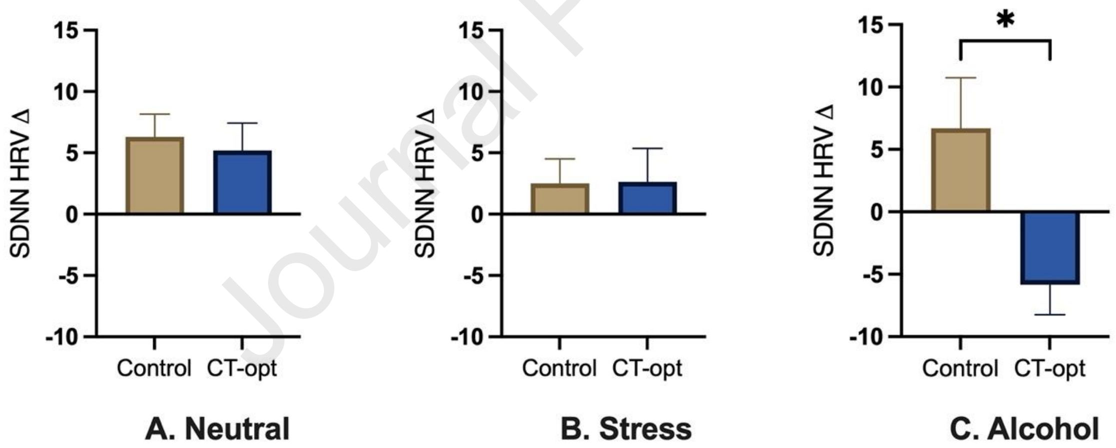

Fig. 2 The mean change of the SDNN HRV between the baseline of the session and the visual stimuli exposure. The data is expressed as mean of the change. Positive values indicate increase of the HRV, whereas negative values indicate decrease. The chance is calculated by subtracting the SDNN HRV of the five-minute epoch of the visual stimuli exposure from the SDNN HRV of a five-minute epoch at the baseline of the session. The error bar indicates SEM. A = neutral visual stimuli. B = stress-inducing visual stimuli, C = alcohol-related visual stimuli, Control = non-CT-optimal treatment, CT-opt = CT-optimal treatment, HRV = heart rate variability, SEM = standard error of means, SDNN = Standard deviation of NN-intervals * = $p < 0.05$.

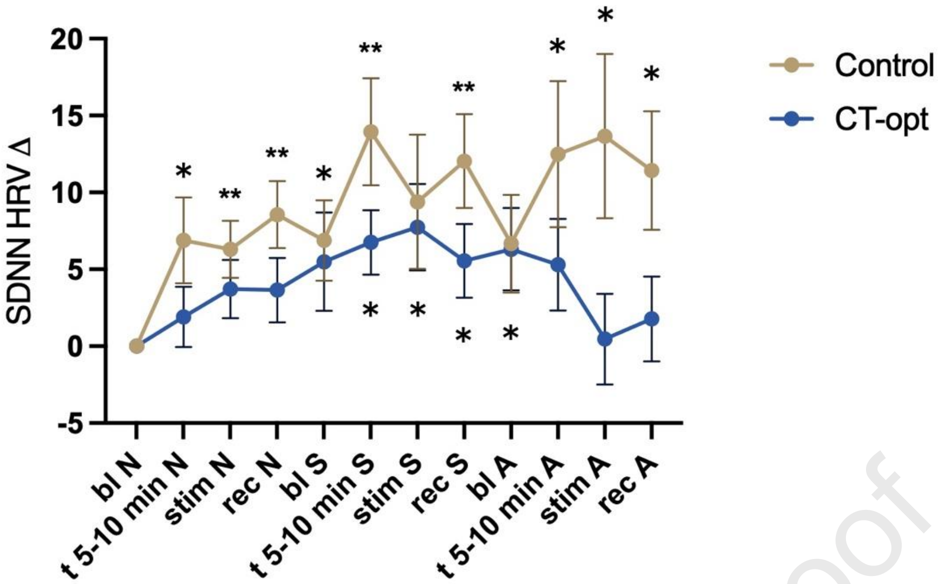

Fig. 3 The mean change of the SDNN HRV throughout the whole experiment. The initial baseline is set as 0. The error bars indicate SEM. The asterisks indicate significant difference from the baseline. Control = non-CT-optimal treatment, CT-opt = CT-optimal treatment, bl = baseline, t 5-10 min = treatment minutes 5 to 10, stim = visual stimulus, rec = recovery, N = neutral stimuli, S = stress inducing stimuli, A = alcohol-related stimuli. SEM = standard error of means. * = $p < 0.05$, ** = $p < 0.01$.

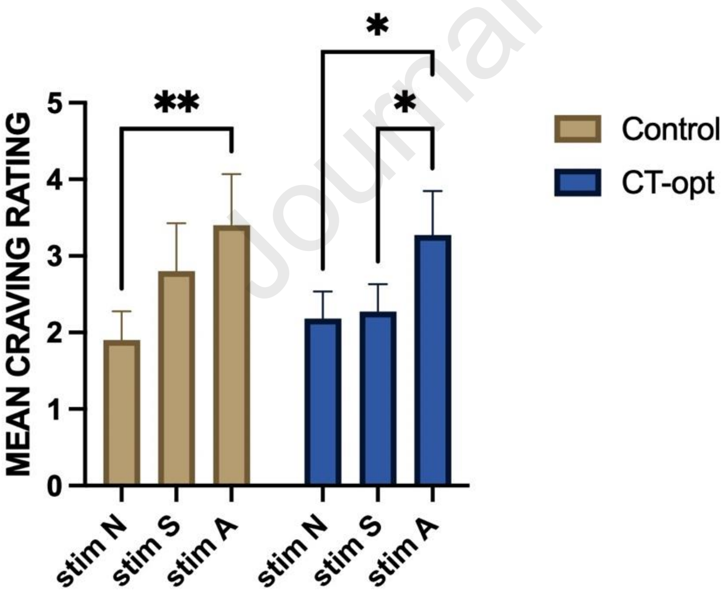

Fig. 4 The mean self-reported craving after each type of visual stimuli exposure. The error bars indicate SEM. Stim N = neutral visual stimuli, stim S = stress-inducing visual stimuli, stim A = alcohol-related visual stimuli. Control = non-CT-optimal treatment, CT-opt = CT-optimal treatment. SEM = standard error of means. * = $p < 0.05$, ** = $p < 0.01$.

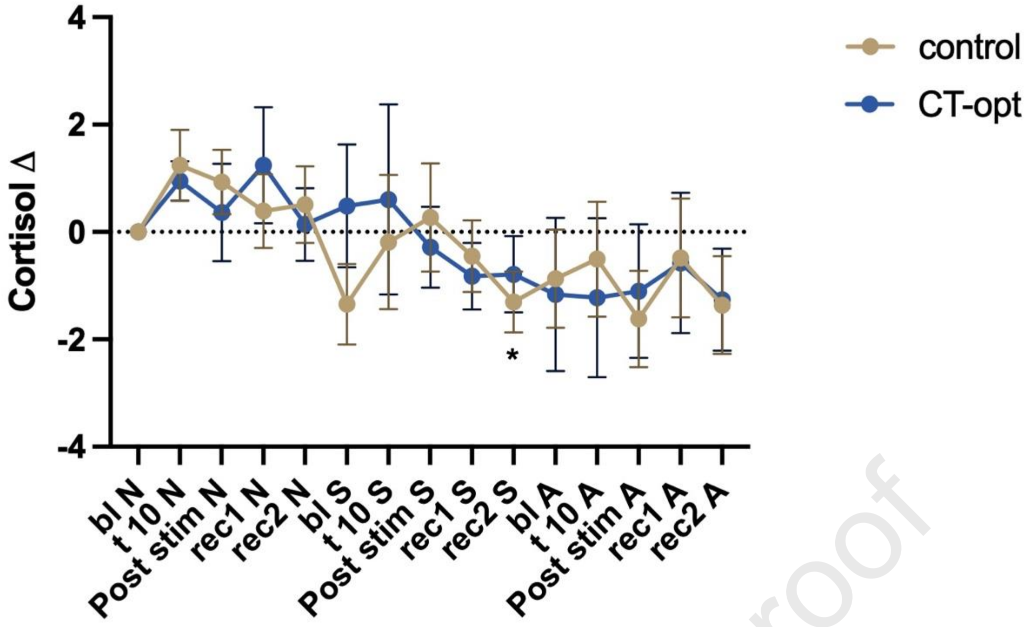

Fig. 5 The mean change of the salivary cortisol throughout the whole experiment. The initial baseline is set as 0. The error bars indicate SEM. The asterisk indicates significant difference from the baseline. Control = non-CT-optimal treatment, CT-opt = CT-optimal treatment, bl = baseline, t 5-10 min = treatment minutes 5 to 10, stim = visual stimulus, rec = recovery, N = neutral stimuli, S = stress inducing stimuli, A = alcohol-related stimuli. SEM = standard error of means. * = $p < 0.05$

- The stress-regulating effects of C-tactile (CT) -optimal touch are known but their therapeutic potential has not yet been investigated in translational studies.
- This study provides the first evidence of clinical relevance of CT-optimal touch in management of substance dependence.
- CT-optimal touch significantly lowers alcohol-cue-elicited heart rate variability, indicating lower relapse susceptibility in alcohol use disorder patients.
- The ability of CT-optimal touch to modulate autonomic cue-reactivity, highlights the potential therapeutic benefits of affective touch in managing alcohol use disorder.