Effects of acupuncture stimulation on brain activation induced by cue-elicited alcohol craving

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Graphical Abstract *HT7 (Shenmen) acupuncture stimulation is associated with reducing cue-elicited alcohol craving by increasing activation in the orbitofrontal cortex and dorsolateral prefrontal cortex and decreasing activation in the left caudate*
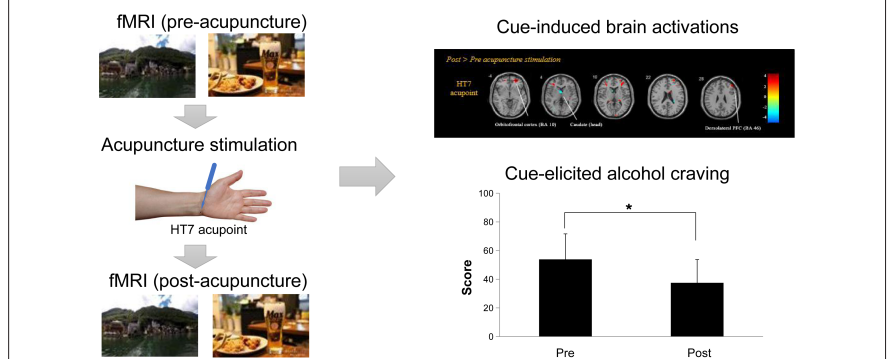
Abstract

Acupuncture has been shown to be effective on alcohol use disorder. However, the underlying mechanism remains poorly understood. To investigate the effects of *Shenmen* (HT7) acupoint on brain activation induced by cue-elicited alcohol craving, 30 right-handed healthy light to moderate alcohol drinkers were recruited from the community. They were randomly assigned to undergo acupuncture either at HT7 (experimental acupoint, *n* = 15) or *Jingqu* (LU8, control acupoint, *n* = 15) acupoints. This randomized controlled study was performed in Daegu Haany University and Daegu-Gyeongbuk Medical Innovation Foundation, Republic of Korea. Recruitment and data collection were conducted from December 2018 to May 2019. The results showed that after acupuncture at HT7 acupoint, the activation of orbitofrontal cortex and dorsolateral prefrontal cortex was greatly increased, while the activation of dorsolateral prefrontal cortex was obviously reduced, and subject's craving for alcohol was reduced when he/she seeing alcohol-related video clips involving various alcohols (beer, wine, or soju) or drinking scenarios. Acupuncture at HT7 more greatly reduced subject's alcohol cravings than acupuncture at LU8 acupoint. These findings suggest that acupuncture can improve the self-control of mild to moderate social drinkers through the activation of the orbitofrontal cortex and dorsolateral prefrontal cortex, thereby reducing the craving for alcohol. The study protocol was approved by the Institutional Review Board of Daegu Haany University Korean Medicine Hospital, Republic of Korea (approval No. DHUMC-D-18026-PRO-02) on November 30, 2018.

Key Words: acupuncture; addiction; alcohol; brain activation; craving; cue; functional MRI; *Shenmen* (HT7) acupoint

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Introduction

Craving for drugs as an intense conscious desire to take substances such as psychostimulants, alcohol, and nicotine, is a central feature of addiction (Sayette, 2016; Treloar Padovano et al., 2019; Suzuki et al., 2020). Drug-associated cues have been implicated in inducing craving for drugs (Myrick et al., 2004; McHugh et al., 2016), which is associated with motivationally relevant withdrawal symptoms and eventually leads to relapse (Baker et al., 2006). Therefore, it seems reasonable to propose that a therapeutic intervention to manage cravings might contribute to the reduction in vulnerability to relapse after long abstinence (George et al., 2001; Karch et al., 2015).

Neuroimaging studies have investigated brain regions involved in alcohol cue-elicited craving in patients with alcohol use disorder (Modell and Mountz, 1995; George et al., 2001; Heinz et al., 2004; Karch et al., 2015; Fukushima et al., 2020). These finding indicated brain regions activated by cues are associated with reward, memory, cognition and emotion (Myrick et al., 2004; Filbey et al., 2008; Cai et al., 2012). In

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particular, neural reward circuits, precisely mesocorticolimbic dopamine pathways projecting from the ventral tegmental area to the nucleus accumbens and the prefrontal cortex are responsible for the desire to take drugs in addicts (Koob, 1992). On the other hand, the dorsolateral prefrontal cortex (DLPFC), which is involved in the voluntary processing of self-control emotions, and the orbitofrontal cortex (OFC), which is involved in the involuntary processing of self-control emotions, play crucial roles in the reward neural circuit (George et al., 2001; Spreng et al., 2013). Therefore, it can be suggested that the activation of the DLPFC and OFC might help with withdrawal symptoms from alcohol and reduce the cravings as well as the consumption of alcohol.

Since acupuncture, the insertion of thin solid needles into specific human body points, was first proposed as a treatment for addiction in the 1970s (Smith and Khan, 1988), considerable evidence has shown that acupuncture may be an effective complementary and alternative therapy for the treatment of substance use disorders (Smith and Khan, 1988; Grant et al., 2016; Motlagh et al., 2016; Schmidt et al., 2016; Wu et al., 2016; Chen et al., 2018). Many studies have reported that acupuncture at various acupoints such as *Shenmen* (HT7), *Neiguan* (PC6), *Sanyinjiao* (SP6), and *Zusanli* (ST36) were effective in reducing alcohol intake and relieving withdrawal signs in alcohol use disorder (Kang et al., 2017; Yang et al., 2017; Chen et al., 2018). Interestingly, HT7 stimulation has been shown to work in the brain to affect the mesolimbic dopamine pathway (Kang et al., 2017; Chen et al., 2018).

Functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS), as a non-invasive and high spatial resolution neuroimaging, are especially valuable for evaluation of acupuncture that influences neural activity in human brain regions related to a particular behavioral function (Cai et al., 2012; Li et al., 2018; Fernandez Rojas et al., 2019; Ghafoor et al., 2019). In particular, a fMRI study has demonstrated that acupuncture at HT7 acupoint activated brain areas related with self-control such as the prefrontal cortex and increased alcohol abstinence self-efficacy in social drinkers (Yang et al., 2017).

Based on these acupuncture effects, the present study was designed to investigate the effect of acupuncture at HT7 acupoint on brain activation induced by cue-elicited craving for alcohol.

Participants and Methods

Participants

This randomized controlled study was performed in Daegu Haany University and Daegu-Gyeongbuk Medical Innovation Foundation. Thirty right-handed volunteers who were light to moderate drinkers with an average alcohol consumption of 5.1–30 g/d were recruited from the community (Kim et al., 2017). Recruitment and data collection were conducted from December 2018 to May 2019. The participants had no history of neuropsychiatric disorders and no contraindications for MRI. None of the participants were diagnosed or medicated for alcohol dependence. We randomly assigned 15 subjects each to either the HT7 (Shenmen; experimental acupoint) group or the LU8 (Jingqu; control acupoint) group using a computer-generated randomization list. One researcher created an allocation, enrolled participants, and assigned participants to each group. The participants were required to abstain from alcohol use during at least 1 week before experiment. During the experiment, one participant in the HT7 group was dropped out due to the pain of acupuncture stimulation. One participant in the LU8 group had unusable MRI data due to excessive head movement with axis

displacement > 1.5 mm and head rotation > 1.5° during the scanning. Therefore, 14 participants each were included in the HT7 (eight males and six females; mean age of 21.93 ± 1.73 years) and LU8 groups (eight males and six females; mean age of 22.21 ± 1.43 years) for the final analysis (**Table 1**). Flow diagram for the enrollment of study participants is shown in **Figure 1**.

Table 1 | General characteristics of the participants included in this study

Variables	HT7 group (*n* = 14)	LU8 group (*n* = 14)
Sex (male/female, *n*)	8/6	8/6
Age (yr)	21.93±1.73	22.21±1.42
Alcohol Abstinence Self-Efficacy (score)	51.79±8.16	51.79±13.26
Alcohol Urge Questionnaire (score)	18.43±2.41	18.50±3.74
AUDIT (score)	9.57±3.23	10.07±2.92

The data are expressed as the mean ± standard deviation unless otherwise stated. There were no statistically significant differences in the variables between the HT7 (experimental acupoint) and LU8 (*Jingqu*; control acupoint) groups. AUDIT: Alcohol Use Disorders Identification Test.
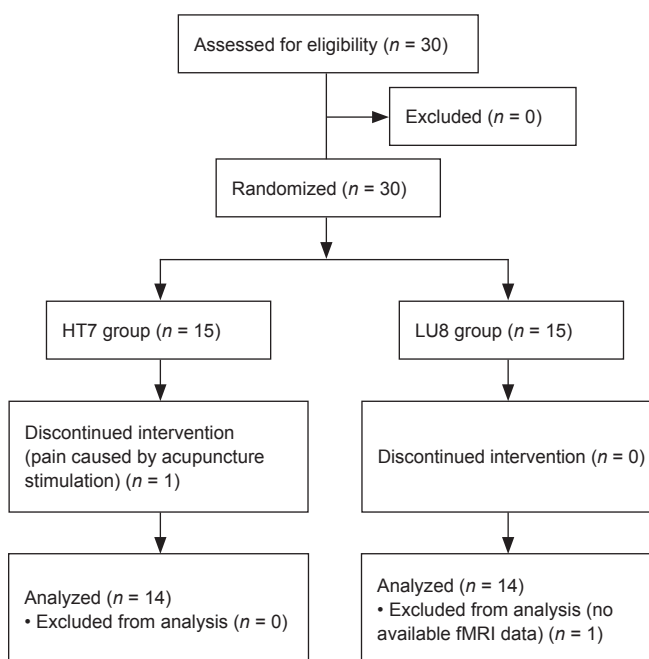

Figure 1 | **Flow diagram for the enrollment of study participants.**

The study protocol was approved by the Institutional Review Board of Daegu Haany University Korean Medicine Hospital (approval No. DHUMC-D-18026-PRO-02) on November 30, 2018. The study was performed in accordance with *Declaration of Helsinki*, and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (**Additional file 1**). All participants signed written informed consent before participation.

fMRI design

The cue-induced MRI scanning procedures were performed before and after acupuncture stimulation. The subjects were examined in the supine position and their heads were restrained by foam cushions surrounding the head. An MRI-compatible Visual System (NordicNeuroLab, Bergen, Norway) and video goggles fixed in place with a head coil were used for presenting the visual stimuli. They were asked to view the video clip carefully during the fMRI scanning. The fMRI paradigm used a block design consisting of five alcohol blocks (experimental condition) alternating with five neutral blocks

(baseline condition). The alcohol blocks presented alcohol-related video clips involving various alcohols (beer, wine, or soju) or drinking scenarios. The neutral blocks showed nature-related video clips. The video clips were created by the authors and supplemental video clips were obtained from Creative Commons licensed video. Each block lasted 20 seconds and consisted of several short video clips. The total duration of the scanning was 3 minutes and 20 seconds (**Figure 2**).

Acupuncture stimulation
After the cue-induced MRI scanning, the participants remained in the scanner in the same position without moving. They were instructed to keep their eyes closed and remain relaxed. The HT7 group received acupuncture stimulation at the left HT7 acupoint (located at the ulnar end of the transvers crease of the wrist, between the flexor carpi ulnaris and the flexor digitrum superficialis), while the LU8 group received acupuncture stimulation at the left LU8 acupoint (located on the anterolateral aspect of the forearm, between the radial styloid process and the radial artery) (Lim, 2010). LU8 acupoint, located at the lung meridian and close to HT7 acupoint, has been clinically used to treat lung-related disorders. LU8 acupoint was chosen as the control acupoint to control for nonspecific effects of mechanical stimulation (Stux et al., 2003). The acupuncture needle (non-magnetic titanium sterile needle 30 mm in length and 0.25 mm in diameter) was inserted vertically into each acupoint to a depth of 0.5 cm. To stimulation, the needle was rotated manually in clockwise and counterclockwise directions at 0.5 Hz during 20 seconds and repeated five times. The total length of the acupuncture stimulation lasted 10 minutes. All acupuncture manipulations were performed by the same licensed Korean medical doctor (**Figure 2**).

Data acquisition
The Magnetom Skyra 3T MRI system (Siemens, Erlangen, Germany) and a standard head coil were used to perform blood oxygenation level-dependent (BOLD) fMRI. The BOLD-weighted Gradient-Echoplanar Imaging (EPI) parameters were acquired using the following parameters: repetition time = 2000 ms, echo time = 30 ms, field of view = 210 mm^2, flip angle = 90°, matrix size = 64 × 64, and slice thickness = 4 mm. Anatomical T1-weighted gradient-echo images were obtained using the following parameters: repetition time = 250 ms, echo time = 2.86 ms, flip angle = 70°, a 1-mm slice thickness, a matrix size of 128 × 128, and a field of view of 210 mm. All images were acquired parallel to the anterior commissure-posterior commissure plane.

fMRI data analysis
The imaging data were analyzed using statistical parametric mapping software (SPM 8: Wellcome Department of Cognitive Neurology, London, UK) in the MATLAB environment (The Mathworks, Natick, MA, USA). All functional images underwent realignment to correct for head motions. Then, the realigned images were spatially normalized using the standard Montreal Neurological Institute (MNI) template based on the standard stereotaxic coordinate system. The images were subsequently smoothed spatially with a Gaussian kernel of 8 mm full width at half-maximum (FWHM) to improve the signal-to-noise ratio. The first level of analysis for each subject's contrast images (alcohol block minus neutral block) was conducted to investigate the individual brain activation maps. The second level of analysis using paired t-tests was performed to compare the cue-induced activation differences between pre- and post-acupuncture stimulation. Statistical parametric maps were obtained, and the statistics threshold was set at $P < 0.001$ for the uncorrected level with at least five contiguous voxels forming a valid cluster.

Measures of cue-elicited alcohol craving
Before and after the fMRI session, self-rated alcohol craving elicited by visual stimuli was assessed to determine the effect of acupuncture stimulation outside the scanner. The visual stimuli consisted of 10 alcohol-related and 10 neutral pictures. The alcohol-related pictures were selected from copyright-free images or were taken by the authors of the study. Neutral pictures were obtained from the International Affective Picture System (IAPS) (Lang et al., 1997). Each picture was rated on a 10-point Likert scale, ranging from 'not at all' (0 points) to 'extremely' (10 points) according to the intensity of alcohol craving. The pictures were presented in a random order. The scores for alcohol-related and neutral pictures were classified, and the total scores for cue-elicited alcohol craving were calculated by summing the craving ratings for each of the 10 pictures. The total scores ranged from 0 to 100, with higher total scores indicating more intense alcohol cravings elicited by the visual stimuli.

Statistical analysis
Sample size was calculated based on a previous acupuncture and fMRI study for brain functional analysis (Cai et al., 2012). Therefore, we recruited 15 subjects per group, considering for a 20% dropout rate. Statistical analysis was performed using SPSS version 12.0 (SPSS, Chicago, IL, USA). The data were analyzed by the Shapiro-Wilk test for normality and are presented as the mean ± SD. The interaction effects of groups (HT7 and LU8) and time (pre- and post-acupuncture stimulation) were analyzed using two-way repeated measures analysis of variance. Independent sample t-tests were conducted to evaluate whether there was a significant difference between the groups in value computed by subtracting pre-acupuncture craving scores from the post-acupuncture craving score. The significance level was set at $P < 0.05$.

Results
Cue-induced fMRI findings
Alcohol cue-induced brain activation was significantly increased on the right superior and middle frontal gyrus (BA 10 and 46) after acupuncture at HT7 acupoint compared to before acupuncture. In addition, alcohol cue-induced brain activation was significantly decreased in the left caudate ($P < 0.001$, uncorrected) after acupuncture at HT7 acupoint compared to before acupuncture. Alcohol cue-induced brain activation was significantly decreased in the bilateral middle temporal gyrus (BA 39) ($P < 0.001$, uncorrected) after acupuncture at LU8 acupoint compared to before acupuncture stimulation (**Table 2** and **Figure 3**).

Alcohol craving analysis
There was a significant interaction effect of group and time in the alcohol-related pictures ($F_{(1,26)} = 6.895$, $P = 0.014$). In the HT7 group, the simple effect of acupuncture stimulation was significant ($F_{(1,13)} = 14.118$, $P = 0.002$). However, in the LU8 group, the simple effect of acupuncture stimulation was not significant ($F_{(1,13)} = 1.000$, $P = 0.336$). However, there was a significant interaction effect of group and time in the nature-related pictures ($F_{(1,26)} = 0.593$, $P = 0.448$). The effect of acupuncture stimulation was significant, indicating that the mean score change for the alcohol-related pictures was higher in the HT7 group (16.36 ± 16.29 points) than that in the LU8 group (2.79 ± 10.42 points) ($t_{(26)} = 2.626$, $P = 0.014$). However, there was no significant change in scores for the nature-related pictures ($t_{(26)} = -0.770$, $P = 0.448$) between the HT7 (1.14 ± 2.28 points) and LU8 groups (2.5 ± 6.19 points) (**Table 3**).

Table 2 | Significant differences in brain activation induced by visual alcohol cues pre- and post-acupuncture stimulation

Brain region	Brodmann area	Peak MNI coordinates (mm)			Peak *t*-value	No. of voxels
		x	y	z		
HT7						
Pre-acupuncture < post-acupuncture						
Right superior frontal gyrus	10	26	54	−4	4.61	28
Right middle frontal gyrus	46	48	42	28	4.33	9
Pre-acupuncture > post-acupuncture						
Left caudate head		−6	10	4	5.20	13
LU8						
Pre-acupuncture < post-acupuncture						
No	−	−	−	−	−	−
Pre-acupuncture > post-acupuncture						
Right middle temporal gyrus	39	50	−62	22	4.73	24
Left middle temporal gyrus	39	−44	−58	10	4.40	27

P < 0.001, uncorrected. HT7: *Shenmen* (experimental acupoint); LU8: *Jingqu* (control acupoint). "−" Means no activation.

Table 3 | Changes in visual cues-elicited alcohol cravings caused by acupuncture stimulation

Type of visual cue	HT7 group			LU8 group		
	Pre-acupuncture	Post-acupuncture	*P*-value	Pre-acupuncture	Post-acupuncture	*P*-value
Alcohol	53.86±17.79	37.50±16.20	0.002*	48.00±14.72	45.21±17.57	0.336
Nature	2.79±5.69	1.64±4.33	0.084	5.50±9.73	3.00±5.84	0.154

Cue-elicited alcohol craving was assessed using a 10-point Likert scale. Data are expressed as the mean ± SD. *Significant simple main effect of acupuncture stimulation (*P* < 0.05). HT7: *Shenmen* (experimental acupoint); LU8: *Jingqu* (control acupoint).
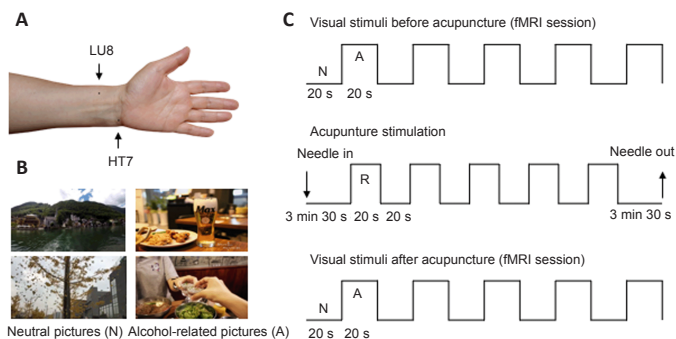

Figure 2 | Experimental protocol.
(A) Location of acupoint HT7 (*Shenmen*; experimental acupoint) and LU8 (*Jingqu*; control acupoint). (B) Example of neutral pictures (N) and alcohol-related pictures (A) used to elicit alcohol cravings. (C) Diagram of fMRI. The fMRI block design consisted of five neutral blocks (N, neutral-related video clip) alternating with five alcohol image blocks (A, alcohol-related video clips) for cue-induced reactivity. R indicates that needle was rotated manually in clockwise and counterclockwise directions at 0.5 Hz.
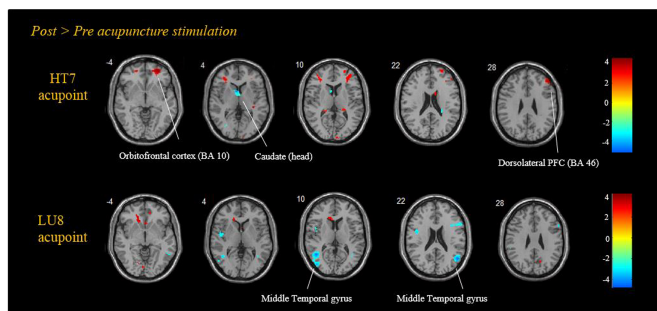

Figure 3 | fMRI changes in alcohol cue-induced brain activation pre- and post-acupuncture stimulation.
Acupuncture at HT7 (*Shenmen*; experimental acupoint) significantly increased activation in the orbitofrontal cortex (BA 10) and dorsolateral prefrontal cortex (PFC) (BA 46), significantly decreased activation in the left caudate (*P* < 0.001, uncorrected) after acupuncture stimulation compared to before stimulation. After LU8 (*Jingqu*; control acupoint) acupuncture, however, alcohol cue-induced brain activation was significantly decreased in the bilateral middle temporal gyrus (BA 39) (*P* < 0.001, uncorrected) compared to before acupuncture.

Discussion

This fMRI study investigated the immediate effects of acupuncture stimulation on the brain activation of alcohol craving in social drinkers. The present results demonstrated that HT7 acupuncture significantly increased brain activation in the OFC (BA10) and DLPFC (BA46) but decreased brain activation in the caudate nucleus, a structure implicated in the mesolimbic dopamine pathway. Post-acupuncture stimulation in the HT7 group exhibited significant decreases in the alcohol craving scores compared to the pre-acupuncture stimulation. These results are supported by the previous study showing that increased brain activation in the OFC and DLPFC could improve self-control emotions and in turn reduce craving for alcohol (Boggio et al., 2008). In addition, a significant negative correlation was found between decreased activation of caudate nucleus and increased activation of DLPFC during cue-elicited craving of smoking, suggesting that this negative coupling could reduce cravings (Yuan et al., 2017). Given these findings, it can be suggested that HT7 acupuncture play a role in reducing craving for alcohol via direct activation of brain pathway.

Many neuroimaging studies have reported brain activation in alcohol craving (Modell and Mountz, 1995; George et al., 2001; Heinz et al., 2004; Karch et al., 2015; Fukushima et al., 2020). In 1995, Modell and Mountz reported that increased blood flow in the right caudate nucleus was associated with the induction of alcohol cravings in alcoholics in Single-photon emission computed tomography (SPECT) study. In 2001, George et al. found that the DLPFC and anterior thalamus were associated with craving in 10 alcoholic subjects. Heinz et al. (2004) found that increased activation of the left caudate nucleus occurred in alcohol-dependent subjects while viewing alcohol-related images. In 2015, Karch et al. demonstrated that activation of the DLPFC region was significantly decreased during cue-elicited craving in 13 patients with alcohol use disorder compared to 14 control subjects in an fMRI study.

Acupuncture at *Shenmen* (HT7) acupoint on the heart channel is frequently used to treat mental and psychiatric disorders

including drug abuse. We have previously demonstrated that acupuncture at HT7 acupoint, but not control acupoint, attenuated alcohol seeking behavior in alcohol dependent rats through activation of endorphinergic afferents to the nucleus accumbens to the arcuate nucleus of the hypothalamus (Chang et al., 2019) and relapse to cocaine seeking behavior via activation of ventral tegmental area GABA neurons in extinguished rats (Jin et al., 2018). These results suggest that these effects are specific to HT7 acupoint. Thus, HT7 acupoint were chosen to determine the effects of acupuncture on brain activation and cue-elicited craving for alcohol. The LU8 acupoint used to treat disorders of the respiratory organs was employed as a control acupuncture acupoint to control for the possibility of generalized effects of acupuncture. The present study shows that acupuncture at HT7 acupoint reduces cue-elicited craving via the regulation of brain activity. As acupuncture at other acupoints modulates cue-elicited drug craving and brain activation (Cai et al., 2012; Wang et al., 2019), we can speculate that stimulation of different acupoints may produce significant effects on the activity of craving-related brain areas and cue-elicited alcohol craving in drug addicts. It would be interesting to assess the effects of acupuncture at other acupoints on cue-elicited alcohol craving.

Several fMRI studies have reported the effects of acupuncture therapy on brain activation related to cue-elicited craving in patients with substance use disorder (Cai et al., 2012; Kang et al., 2013; Theodoratou et al., 2014; Yang et al., 2017). In 2012, Cai et al. demonstrated that acupuncture at Zusanli acupoint (ST36) could suppress the activation of craving-related brain regions in the frontal lobes (Cai et al., 2012). The next year, Kang et al. (2013) reported that acupuncture at HT7 caused decreases in the activation of the prefrontal cortex, amygdala, and hippocampus and reduced the subjective cravings of 25 smokers. Taken together, these results imply that acupuncture may reduce craving for drugs by modulating the activation of brain areas related to cue-elicited drug craving. Using fMRI, Yang et al. (2017) investigated the effects of acupuncture at HT7 on the activation of brain regions in 34 healthy social drinkers. Importantly, the results showed that acupuncture at the HT7 acupoint induced the activation of the inferior frontal gyrus implicated in self-control emotion and increased alcohol abstinence self-efficacy. Given a role for inferior frontal gyrus in self-control, this suggests the possibility that acupuncture at the HT7 acupoint may reduce craving for alcohol by improving self-control over craving. As acupuncture at the HT7 acupoint inhibited alcohol-induced dopamine release in the nucleus accumbens and suppressed the reinforcing effects of alcohol (Yang et al., 2010), we speculate that activation of brain areas related to self-control by acupuncture might contribute to its ability to reduce alcohol cravings. In support of this finding, the present results demonstrated that acupuncture at the HT7 acupoint significantly increased the activation of the OFC and DLPFC but decreased the activation of the caudate nucleus, in response to cue-elicited alcohol craving. Also, acupuncture significantly decreases the alcohol craving scores. These results suggest that acupuncture may attenuate alcohol craving by ameliorating self-control through the activation of OFC and DLPEC. However, this study has several limitations. The recruited subjects were social drinkers (light to moderate) and acupuncture stimulation was conducted in a single session. Thus, we could not confirm the long-term effects of acupuncture stimulation. Also, the number of participants is low. Therefore, further studies to overcome the above limitations should be encouraged.

In conclusion, we demonstrated the immediate effects of acupuncture stimulation on cue-induced brain activation and alcohol cravings. This study opens the possibility that acupuncture at HT7 acopoint can be effective for reducing alcohol cravings in people with alcohol use disorder.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	-
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	-
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9

Results

Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5
	13b	For each group, losses and exclusions after randomisation, together with reasons	5
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-

Discussion

Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13

Other information

Registration	23	Registration number and name of trial registry	-
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.