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Chess-based cognitive remediation training as therapy add-on in alcohol and tobacco use disorders: protocol of a randomized, controlled study

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Abstract

Introduction

Alcohol and tobacco use disorders (AUD, TUD) are frequent, both worldwide and in the German population. While cognitive dysfunctions might also be a predisposing factor for the development and maintenance of AUD and TUD, these disorders also lead to cognitive impairments facilitating instances of relapse. Cognitive training has been proposed as an intervention for enhancing cognitive functioning and improving treatment outcome. However, possible cognitive enhancement effects and underlying neural mechanisms of these cognitive interventions are not yet fully understood. Examining the effect of chess-based cognitive remediation training (CB-CRT) on treatment outcomes, such as abstinence or reduced substance consumption, will provide insights into mechanisms underlying relapse and abstinence, including potential risk factors. If CB-CRT as a therapy add-on proves to be more effective than standard treatment alone, this intervention might help to improve health behaviour in affected individuals.

Methods

This study evaluates CB-CRT as a therapy add-on for individuals with AUD and TUD. N=96 individuals with either AUD (N=48) or TUD (N=48) between the ages of 18 and 65 years will be randomized to four treatment groups. Two control groups with 24 AUD and 24 TUD individuals will receive treatment as usual, i.e., AUD treatment in a clinic, TUD outpatient treatment. Two therapy add-on groups with 24 AUD and 24 TUD individuals will receive a 6-week CB-CRT as a therapy add-on to their treatment as usual. Several neurocognitive tests as well as functional magnetic resonance imaging (fMRI) tasks will be administered before and after the 6-week period of CB-CRT or corresponding time frame with regards to the control group. All individuals will be followed up on monthly for three months. Endpoints of this study include relapse and substance intake but also effects of group and time regarding neural activation during fMRI tasks, as well as performance on several neurocognitive tests.

Trial registration

The study was registered in the Clinical Trials Register (trial identifier: NCT04057534) on December 8th, 2019.

Strengths and Limitations of this study

- The evaluation of the efficacy of CB-CRT as a supportive therapy add-on for SUD might lead to cost-efficient positive treatment outcomes.
- The use of objective measures to examine underlying neurobiopsychological mechanisms expands the current research on risk factors for relapse.
- The inclusion of two substances (alcohol and tobacco) increases the generalizability of the findings.
- The 6-week long therapy add-on might lead to drop-outs due to the large amount of time participants have to commit to the program.

Introduction

Substance use, including alcohol and tobacco use, is widespread both worldwide and in the German population. Worldwide, the prevalence for heavy episodic drinking of alcohol was estimated at 18.4% for adults, while daily smoking was estimated at 15.2%[1]. In 2018 in Germany, the prevalence of hazardous consumption of alcohol was estimated at 19.1%, and the 12-month prevalence for alcohol use disorder (AUD) at 5.9%. The prevalence of daily consumption of tobacco was estimated at 15.1%, and the 12-month prevalence for tobacco use disorder (TUD) at 8.6%[2]. In Germany, follow-up costs of alcohol use are estimated at 21 billion euros[3] and for tobacco use at 24 billion euros[4]. Furthermore, negative effects on health and on mortality rates are associated with TUD[5].

For individuals with AUD having undergone treatment, relapse rates between 22 and 86% have been observed during short-term follow-ups (16 weeks) up to a long-term follow-up of 16 years[6-8]. Following treatment, the relapse rate for TUD after one year is estimated to be between 2 and 17%[9]. A relapse can be brought on by heightened stress sensitivity, depressive mood, increased anxiety, or confrontation with a substance-related stimulus[10-12].

Even though some studies postulate intact, goal-directed behaviour in individuals with SUD [13-15], others observed neurobiological impairments in brain areas involved in inhibitory control in individuals with SUD[16-19]. In a model proposed by Bechara, SUD is viewed as an imbalance between two distinct, but closely interacting neural systems[20], which are essential for decision-making: The impulsive system is involved in the prediction and valuation of immediate rewards and includes such regions as the amygdala and the striatum. The reflective system signals long-term consequences of actions and involves the ventromedial prefrontal cortex (VMPFC), the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate, the insula, and the hippocampus. In SUD, it is assumed that the impulsive system becomes overactive, preventing the reflective system from exerting executive cognitive control over substance use. It might be those immediate rewards, such as pleasant effects derived from alcohol or nicotine consumption, are overvalued, and give preference over future rewards, such as health benefits associated with abstinence. Individuals with SUD also demonstrate a preference for smaller, immediate monetary rewards over larger, delayed ones[21]. Furthermore, the imbalance between impulsive and reflective systems reveals itself in dysfunctional inhibitory control, leading to increased risk taking[20]. Beyond these

impairments, individuals with SUD also demonstrate reduced cognitive functioning in the domains of problem solving, mental flexibility, forming judgments, and working memory[22]. A study using functional magnetic resonance imaging (fMRI)[23] found less activation in the right frontal cortex during a response inhibition task was associated with more cigarettes smoked in participants wanting to quit smoking. Other studies using fMRI have revealed a shift of neural activation from the ventral (nucleus accumbens) to the dorsal striatum (putamen and nucleus caudate), which was suggested to reflect a decrease in cortical control when viewing substance related cues [24]. Being related to executive functions, metacognitive abilities and beliefs play a major role in addiction[25]. In general, metacognition refers to the ability to know about cognition in general but, more importantly, to be aware of and know about one's own cognition[26]. Prefrontal regions, as well as the precuneus or dorsal anterior cingulate cortex seem to play an important role[27]. Generic and dysfunctional metacognitive beliefs, but also metacognitive beliefs about addiction-related thoughts or craving can predict the severity of addictive behaviour, craving, and relapse[25].

„Cognitive remediation" (Cognitive remediation therapy (CRT)) is a psychotherapeutic approach to improve cognitive deficits[28]. Cognitive training exercises span functional domains from executive functioning (inhibition, decision-making, cognitive flexibility, and working memory) to attention. Through repeated training, CRT can systematically stimulate and strengthen cognitive processes. A primary therapeutic objective is to improve the efficacy of other psychotherapeutic interventions, which require a minimal level of cognitive skill[29]. For example, it has been demonstrated that executive functioning skills can influence the efficacy of cognitive behavioural therapy[30]. CRT, specifically, has already been demonstrated to be successful as an add-on therapy in treating schizophrenia and eating disorders[31]. However, it has been suggested to explicitly teach metacognitive abilities in order to improve the outcome of CRT[32], since this might be a significant mechanism contributing to the effects of CRT in patients with schizophrenia[33]. Indeed, recent observations indicate a beneficial effect of CRT on metacognitive abilities, e.g., in schizophrenia[34]. As an add-on therapy to treat substance use disorders CRT seems equally promising[35]. However, there is a lack of studies examining the efficacy of CRT as a modulator of cognition to improve treatment outcomes[36]. A review on AUD[37] discussed that CRT improves split attention, recognition of warning signals, working memory, as well as episodic memory. Most relevantly, an improvement in working memory and inhibitory control was able

to exert a positive influence on substance use patterns[37]. Additionally, including metacognitive trainings when treating individuals with SUD might be advantageous[25, 38]. Finally, promising studies have demonstrated a potential beneficial effect of classical chess training on the treatment of attention deficit hyperactivity disorder (ADHD) and schizophrenia as an add-on therapy. In the case of ADHD, classical chess training was able to effectively reduce disease severity[39]. A further study in patients with ADHD showed an improvement in the ability to concentrate[40]. Negative symptoms common to patients suffering from schizophrenia include a wide variety of cognitive deficits, including impaired attention-, memory-, learning- and problem-solving skills[41]. Chess training was able to rescue some of these deficits experienced by schizophrenic patients, improving voluntary processing, inhibitory capacity and planning proficiencies[42]. Examining the effects of chess training on mathematical problem-solving and metacognitive abilities in school children, no significant effects were observed compared to an active control group playing checkers and a passive control group[43].

Besides the known effects of CRT on metacognition, the beneficial effect of chess-based CRT still remains unclear. However, present findings suggest that chess-based CRT might be able to improve cognitive functioning in domains which can be improved by classical CRT, while simultaneously potentially improving specific domains modulated by chess-based interventions.

Consequently, our study aims to assess the effects of chess-based CRT (CB-CRT) on treatment outcomes and different aspects of cognition in individuals with AUD and TUD. Further, we assess underlying neurobiological mechanisms of CB-CRT in AUD and TUD also in relation to treatment outcome.

Method and Analyses

To investigate the effects of CB-CRT as a therapy add-on in alcohol and tobacco use disorders, N = 96 individuals will be examined. N = 48 AUD participants undergoing a qualified therapy or rehabilitation treatment for alcohol use disorder and N = 48 TUD participants who participate in a qualified smoking cessation group therapy will be included in the study. The Consolidated Standards Reporting Trials (CONSORT) statement was used for developing the study framework. Individuals with a diagnosis of AUD will be recruited from the out-patient

and in-patient clinics of the Department of Addictive Behaviour and Addiction Medicine at the Central Institute of Mental Health and from the residential addiction treatment center MEDIAN Klinik Wilhelmsheim, Germany. Individuals with TUD will be recruited using public announcements including, flyers, and social media posts.

Half of each group (AUD, TUD) will be randomly assigned to either the control group or experimental group. Regarding the control groups, N = 24 AUD participants receive an in-patient qualified detoxification treatment program, an in- or out-patient rehabilitation program, or semi-inpatient therapy in a day-clinic. N = 24 TUD participants receive qualified smoking cessation group therapy following study inclusion. The out-patient smoking cessation therapy lasts for 6 weeks with one group therapy session à 1.5 hours per week. Individuals randomly allocated to the experimental group (24 individuals with AUD and 24 individuals with TUD) will receive CB-CRT for 1.5 hours twice a week for 6 weeks in addition to the standard treatment.

Examination procedure

Eligible participants between 18 and 65 years will be informed about the purpose and all aspects of the study. They will be provided with written study information according to the ethics regulations. Participants will be able to ask questions regarding the study. Afterwards, written informed consent will be obtained. All participants can withdraw their consent at any time. Then, study exclusion- and inclusion criteria will be examined. To do so, a structured clinical interview (SCID-5-CV)[44] will be performed to assess a possible history of lifetime and current mental disorders. Individuals with a diagnosis of severe mental or personality disorders will be excluded, e.g., lifetime bipolar disorder or schizophrenia or current severe depression, post-traumatic stress disorder. Current mild or moderate mental or personality disorders, such as mild anxiety-, adaptation, personality disorders or depression, will be tolerated. Individuals with AUD are included in the study after controlled abstinence for at least 72 hours, including completion of medically supervised detoxification (treatment of withdrawal symptoms with short-acting benzodiazepines or chlormethiazole must have been completed for at least three days). Individuals with TUD will be included following the intention to quit smoking. A detailed list of all inclusion and exclusion criteria regarding AUD and TUD are shown in table 1). Following study inclusion, participants will be randomly assigned to either the control or experimental group.

At the baseline examination appointment (T1) all participants will provide sociodemographic information and perform several neuropsychological tasks. An fMRI assessment will then take place. Participants will also fill out several questionnaires directly after the baseline assessment. After the 6 week long intervention period - either standard treatment alone or with CB-CRT as therapy add-on - a second examination appointment (T2) takes place. All participants will perform the same neuropsychological tasks again and the same fMRI assessment as conducted in T1 will take place. Participants will also fill out the same questionnaires as for T1. During a follow-up period of 12 weeks following the intervention, three telephone interviews (FU1, FU2, T3) will be conducted once a month. Instances of relapse and amount of tobacco or alcohol consumption will be documented. Beyond this, the same questionnaires as for T1 and T2 will be completed.

Please see figure 1 for a detailed description of the study procedure and table 2 for list of assessments used, including fMRI and neuropsychological paradigms, and questionnaires.

Standard Treatment

All study participants (TUD and AUD) will follow their respective treatment as usual (TAU). With regards to TUD, a qualified smoking cessation group therapy with one therapy session per week (90 minutes) will be held by a trained and certified psychologist. This intervention is strongly recommended in the latest version of the S3 guidelines for tobacco use disorder[45]. A superior effect on smoking cessation was observed following group therapy compared to, e.g., self-help or less intense interventions[46]. During the qualified smoking cessation group therapy, interventions following a cognitive-behavioural psychotherapy approach will be applied[47]. Study participants with AUD will follow the respective in-house or day-clinic therapeutic programme, as recommended by the respective S3 guidelines for alcohol use disorder[48]. This standard treatment includes medical and psychological interventions.

Chess-based cognitive remediation training

The planned CB-CRT „Entrenamiento cognitivo a través del ajedrez (ECAM, „Cognitive training through chess“, https://ajedrezmagic.es/el-entrenamiento-cognitivo-a-traves-del-ajedrez/) consists of a battery of tasks and was developed by one of the co-authors (J. A. M.). The training battery, which is administered in a group setting using mainly a chess demonstration board, is designed to strengthen cognitive functioning in specific domains such as selective

attention (figure 2a), short-term memory (figure 2b), focal attention, pattern recognition, visuospatial abilities, planification skills (figure 2c), and inhibition. Overall, metacognitive abilities are trained, e.g., by explicitly teaching different concepts of cognitive functioning, questioning, and identifying the underlying cognitive process, and enhancing the awareness of before mentioned aspects. Participants perform most of the specific tasks in front of the group and, for a social reinforcement effect, everyone will applaud the respective participant. Some of the tasks are conducted via paper-pencil. The training battery has been utilized for more than ten years by J.A.M and his colleagues as an add-on therapy for elderly individuals, children with autism and/or ADHD, individuals with Down Syndrome, mental and other disorders, and in adults with SUD. The scientific evaluation of the program is one of the goals of the current study.

In an unpublished pilot study in the rehabilitation clinic at Comunidad Terapéutica La Garrovilla, N = 26 patients with SUD (N = 22 male; substances: alcohol, opiates, cocaine, benzodiazepines, cannabis) were examined. CB-CRT was applied in a group setting twice a week for a duration of 90 minutes each. Cognitive functioning, especially in executive functions, was assessed at admission to the clinic at Comunidad Terapéutica La Garrovilla, Badajoz (Extremadura, Spain) and again after 14 weeks. The neuropsychological testing battery included measures of general processing speed (trail-making test A), cognitive flexibility (trail-making test B)[49], planning abilities (Tower of London)[50] and intelligence (Wechsler Adult Intelligence Scale, WAIS). Significant increases in performance were found after 14 weeks of treatment in general processing speed (trail-making test A; p = .001), cognitive flexibility (trail-making test B; p = .013), the Tower of London test (p = .001) as well as in the WAIS measures for verbal comprehension (“similarities”, p = .019) and for working memory (“letter-number sequencing”, p = .030, “digit span forward”, p = .044, “digit span backward”, p = .018, “digit span total”, p = .007). Performance in the WAIS measures “coding” (processing speed) and “matrix reasoning” (perceptual reasoning) did not differ significantly. In another sample of N = 15 patients receiving the chess-based add-on treatment for 3.5 months, subjective satisfaction was evaluated. On scales ranging from 1 (very unsatisfied / very poor) to 4 (very satisfied / very good), 73% of the patients rated the overall program as very good (i. e. score of 4). 67% of the patients found the program very helpful in treating their SUD (score of 4), 27% found it helpful (score of 3). Further, when asked how the program influenced other domains being negatively affected by SUD before admission, 53% found the

program very supportive (score of 4), 27% found it supportive (score of 3). Besides this, 87% reported that the program helped them to increase their memory capabilities, 93% stated a subjective increase in attention performance, and 93% reported an enhancement in decision-making.

Self-rating Questionnaires

A goal attainment scale[51] will be used to assess abstinence-related goals. Self-esteem will be measured with the Rosenberg scale[52]. Self-efficacy will be assessed with the General Self-Efficacy Scale (GSE)[53]. Perceived Social Support will be examined using the brief form of the Perceived Social Support Questionnaire (F-SozU)[54] and psychological well-being with the Habitual Subjective Well-Being Questionnaire (HSWBS)[55]. Life satisfaction will be measured with the Satisfaction with Life Scale (SWLS)[56]. Affect will be measured with the Positive and Negative Affect Schedule (PANAS)[57]. The symptoms of anxiety will be assessed with the State-Trait Anxiety Inventory[58] as a personality trait (STAI X2) and as a temporary state (STAI X1) whereas depressive symptoms will be measured with Beck Depression Inventory (BDI-II)[59, 60]. Perceived stress will be measured by the Perceived Stress Scale (PSS)[61]. Impulsivity will be measured with the Barratt Impulsiveness Scale (BIS-15)[62, 63]. In addition to impulsivity, the presence of ADHD symptoms will be measured using the Adult ADHD Self-Report Scale-V1.1 Symptoms Checklist (ASRS-V1.1)[64] and the ADHD Self-Rating Scale (ADHD-SB)[65]. A self-report measure of habitual routines and automatic tendencies in everyday life will be done by the Creature of Habit Scale (COHS)[66]. Substance-related habits will be measured by the Self-Report Habit Index (SRHI)[67]. The intensity of physical addiction to nicotine will be assessed by Fagerström Test for Nicotine Dependence (FTND)[68]. As a brief screening test for measuring heavy drinking, active alcohol abuse as well as dependence, the Alcohol Use Disorder Identification Test (AUDIT)[69] will be applied. Alcohol-related withdrawal symptoms will be assessed by clinical institute withdrawal assessment for alcohol scale (CIWA-Ar)[70]. Alcohol or tobacco consumption and craving will be measured with the following self-report scales: Obsessive Compulsive Drinking Scale (OCDS-G)[71], Alcohol Craving Questionnaire (ACQ-SF-R)[72], Craving Automated Scale for Alcohol (CAS-A)[73], Alcohol Urge Questionnaire (AUQ)[74], Alcohol Dependence Scale (ADS)[75], Form90[76], Questionnaire on Smoking Urges (QSU)[77], Craving Automated Scale for Cigarette Smoking (CAS-CS)[78], Obsessive Compulsive Smoking Scale (OCSS)[79], Smoking Consequences

Questionnaire for Adults (SCQ-A)[80], Wisconsin Smoking Withdrawal Scale (WSWS)[81] and Visual Analog Craving Scales (VACS)[82].

Neuropsychological assessments

Tasks investigating components of working memory (Wechsler Memory Scale-3)[83], decision-making (Iowa Gambling Task)[84], as well as mental flexibility (Dimensional Change Card Sort)[85] and attentional capacity (d2-R Test of Attention)[86] will be administered.

fMRI assessments

During the fMRI scanner examination, study participants will perform a stop-signal task[87], alcohol- and tobacco based cue-reactivity tasks[78, 88], an N-back task[89] and a resting-state MRI. Scanning will be performed with a 3T whole-body tomograph (MAGNETOM Prisma; Siemens, Erlangen, Germany). T2* weighted multi-band echo-planar images (mb-EPI) using a multi-band acceleration factor 6 will be acquired in a transversal orientation 20° clockwise to AC-PC-line covering the whole brain (TR = 869 ms, TE = 38 ms, 60 slices, slice thickness = 2.4 mm, voxel size 2.4 × 2.4 × 2.4 mm, no inter-slice gap, field of view (FoV) = 210 mm, matrix size 88 x 88, acquisition orientation T > C, interleaved slice order, acceleration factor slice = 6, flip angle = 58°, bandwidth = 1832 Hz/Px, prescan normalize, weak raw data filter, LeakBlock kernel, fat sat). This short TE and the 20° flip to AC-PC orientation is chosen to minimize susceptibility artefacts. Scanner sequences are provided by the Center for Magnetic Resonance Research (CMRR), University of Minnesota, Minneapolis, MN, USA (https://www.cmrr.umn.edu/multiband/)[90]. In addition, a T1-weighted 3D MPRAGE (Magnetization Prepared - RApid Gradient Echo) dataset consisting of 208 sagittal slices (slice thickness 1 mm, 1×1×1 mm voxel size, FOV 256 x 256 mm^2, TR= 2000ms, TE = 2.01 ms, TI = 800 ms, flip angle = 8°) will be acquired.

Endpoints

Outcome measurements are the duration until the first severe relapse during the follow-up periods and amount of substance consumption in case of a relapse. Additional endpoints are changes in neural alcohol and tobacco cue-reactivity[78, 88], neural correlates of inhibition (stop-signal task)[91] and working memory (N-back task)[89], as well as functional connectivity within the salience network (SN) and executive control network (ECN) using

resting-state fMRI data. Also, working memory capacity (letter-number sequencing task of the Wechsler Memory Scale-3)[83], impulsivity (Barratt Impulsiveness Scale-15)[62, 63], mental flexibility (Dimensional Change Card Sort)[85], decision-making (Iowa Gambling Task)[84, 92] and attentional capacity (d2-R Test of Attention)[93] are endpoints of interest.

Sample size calculation

Using the software package G*Power[94] sample size was estimated assuming an effect size of f = 0.2 (ANOVA with repeated measures, within- and between subject factors and interactions). In this case, ideal sample coverage would be 24 individuals per group (at 80% power, alpha-level 5%).

Data analysis plan

To analyse psychometric and neuropsychological data, SPSS (Statistics for Windows, Version 22.0. IBM Corp., Armonk, NY) will be used. The various dependent variables will be evaluated using multivariate analyses of variance with repeated measures. In addition, linear regression models will be calculated to examine the influence of confounding variables (for example, severity of tobacco or alcohol dependence) on the observed change in dependent variables. Cox-regression analyses will be conducted to examine the association with relapse. To analyse the fMRI data, SPM12 (Wellcome Department of Cognitive Neurology, London, UK) running under Matlab will be used. The pre-processing pipeline will include motion correction, normalization to the Montreal Neurological Institute (MNI) template, and a spatial smoothing with Gaussian kernel of 8 mm full width at half maximum (FWHM) will be conducted. The pre-processed data will then be used for first- and second-level analyses. On the first level (within-subject), neural activation associated with task conditions (contrasts) will be modelled via a convolution with a canonical hemodynamic response function (HFR) following a general linear model (GLM). A high-pass filter to remove low-frequency components of fMRI time-series will be used. Depending on the fMRI tasks, specific contrasts regarding task conditions will be modeled as described in the above cited literature. On the second level (between-subject) and regarding the effects of group and time, paired t-tests (e.g., pre vs. post intervention within one group) and full factorial models will be used. Additionally, regression models including clinical variables, such as severity of TUD or AUD, will be calculated. To control for multiple statistical testing the probability of a family wise error (FWE) will be set to .05.

Hypotheses

Primary hypotheses

1. CB-CRT improves cognitive functioning in AUD/TUD individuals in comparison to standard treatment alone.
2. CB-CRT improves psychosocial functioning (e.g., HSWBS, SWLS) in AUD/TUD individuals in comparison to standard treatment alone.
3. CB-CRT improves neuronal aberrations present when executing cognitive tasks in individuals with AUD/TUD in comparison to standard treatment alone.
4. CB-CRT influences the treatment process, e.g., time to first severe relapse, for AUD/TUD individuals positively in comparison to standard treatment alone.
5. CB-CRT decreases functional connectivity within the salience network in individuals with AUD/TUD in comparison to standard treatment alone.
6. CB-CRT decreases functional connectivity within the executive control network in individuals with AUD/TUD in comparison to standard treatment alone.

Secondary hypotheses

1. CB-CRT might be more efficacious in individuals with impaired cognitive functioning, low self-esteem, self-efficacy, and social support.
2. Chess as a three-week add-on therapy influences the treatment process, e.g., time to first severe relapse for AUD/TUD individuals moderated and mediated by cognitive, affective, and psychosocial factors.

Ethics and dissemination

The study was approved by the local Ethics Committee of the Medical Faculty Mannheim at the University of Heidelberg, Germany (reference number 2017-647N-MA). Before study inclusion and after a detailed explanation of all procedures, all participants will provide written informed consent. The study was registered in the Clinical Trials Register (trial identifier: NCT04057534) on December 8th, 2019. The study results will be disseminated by peer-review publications and conference presentations. Open-access publication is planned for all peer-reviewed publications. All participants are offered to receive a print of the final, published version of peer-reviewed publications. For protection of personal rights, and due to the sensitivity of the clinical and neuroimaging data, data will not be made publicly available. Upon direct request by other researchers and in mutual agreements (e.g., regarding data

protection), anonymized data can be made available. Upon request, analysis procedures and codes will be shared with other researchers.

Tables

Table 1: Inclusion and exclusion criteria of the overall study sample. Specific criteria for AUD and TUD are highlighted.

Inclusion criteria		Exclusion criteria	
• Age between 18 and 65 years • Normal or corrected to normal vision • Signed written informed consent • Signed consent for data security		• Pregnancy • Positive alcohol test • Common exclusion criteria for MRI (e.g., metal, claustrophobia, epilepsy, adiposity) • Suicidality • Severe cognitive impairments (e.g., dementia) • Severe physical illness • Neurological disorders, history of brain injury • Therapy with methylphenidate within the last 8 weeks • Other mental disorders, except for mild or moderate anxiety-, adaptation-, post-traumatic stress-, personality-, attention deficit / hyperactivity disorders	
AUD	**TUD**	**AUD**	**TUD**
• AUD according to DSM-5 (more than 3 fulfilled criteria) • Currently in therapy for AUD (in-patient or outpatient therapy) • Abstinence from alcohol > 72h	• TUD according to DSM-5 (more than 3 fulfilled criteria) • Participation in smoking cessation therapy	• Other Axis I mental disorder except for mild, moderate or remitted depression, other substance use disorders if AUD is still the main diagnosis • Severe withdrawal symptoms (CIWA-Ar > 7; Sullivan et al. 1989) • Psychotropic medication within the last 14 days except for antidepressants or soporific and intake of medication for treating withdrawal effects until 3 days prior to study participation	• Other Axis I mental disorder except for mild or remitted depression, other mild substance use disorders (i.e., max. of 3 fulfilled DSM-5 criteria in the last 12 months) • Psychotropic medication within the last 14 days except for antidepressants

Note: AUD = Alcohol use disorder; TUD = Tobacco use disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders; MRI = Magnetic resonance imaging

Table 2: Schedule of measurement during study participation.

Measurement time point	**S**		**T1**		**T2**		**FU1**		**FU2**		**T3**	
Baseline	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
Demographic information	x	x	x	x								
Current medication*	x	x	x	x	x	x					x	x
Current somatic or mental conditions*	x	x	x	x	x	x					x	x
Structured Clinical Interview (SCID-5-CV)			x	x								
Smoking history			x	x								
Current smoking behavior*					x		x		x		x	x
Smoking Assessment Interview			x		x						x	
(Current) drinking behavior*		x		x		x		x		x	x	x
CIWA-Ar				x		x						
Current drug use*	x	x									x	x
Urine pregnancy and drugs screening			x	x	x	x						
Breath alcohol test			x	x	x	x						
Breath carbon monoxide test			x		x							
Goal attainment scaling			x	x	x	x						
Neuropsychology	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
MWT-B			x									
LNS-Task			x		x							
D2-R			x	x	x	x						
IGT			x	x	x	x						
DCCS			x	x	x	x						
Magnetic resonance imaging	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
Field-Map			x	x	x	x						
Resting-State			x	x	x	x						
NICUETINE			x	x	x	x						
N-Back			x	x	x	x						
SST			x	x	x	x						
ALCUE			x	x	x	x						
MPRAGE			x	x	x	x						
General questionnaires	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
PANAS			x	x	x	x	x	x	x	x	x	x
HSWBS			x	x	x	x						
GSE			x	x								
Rosenberg			x	x								
SWLS			x	x	x	x					x	x
FSozU			x	x								
Questionnaires - depression and anxiety	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
BDI II			x	x	x	x					x	x
PSS			x	x	x	x					x	x
STAI (X1)			x	x	x	x					x	x
STAI (X2)			x	x								
Questionnaires – impulsivity and ADHD	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
ASRS-v1.1			x	x	x	x						
ADHS-SB			x		x							
BIS-15			x	x	x	x					x	x
COHS			x	x								
Questionnaires - alcohol	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
ACQ-SF-R				x		x						x
ADS				x								
AUDIT	x	x										

AUQ				x		x		x		x				
CAS-A				x		x						x		
OCDS-G				x		x		x		x		x		
SRHI (alcohol)				x		x						x		
VACS for MRI (alcohol)			x	x	x	x								
Questionnaires - tobacco	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**		
OCSS			x		x		x		x		x			
CAS-CS			x	x	x						x			
QSU			x		x		x		x		x			
SCQ-A			x		x						x			
WSWS			x		x						x			
SRHI (tobacco)			x		x						x			
FTND			x	x	x						x			
VACS for MRI (tobacco)			x		x									

Note: S = Screening measurement, T1 = baseline and MRI assessment, T2 = MRI assessment, FU = monthly follow-ups via telephone; T3 = final follow-up via telephone; T = Tobacco use disorder; A = Alcohol use disorder; * self-report.

SCID = Structured Clinical Interview for DSM-5; AUDIT = Alcohol Use Disorder Identification Test; CIWA-AR = Clinical Institute Withdrawal Assessment; MWT-B = Multiple-choice vocabulary test (German version); LNS = Letter-Number-Sequencing (Wechsler-Memory Scale-3); D2-R = d2-R Test of Attention; IGT = Iowa Gambling Task; DCCS = Dimensional Change Card Sort; NICUETINE = fMRI tobacco cue-reactivity task; N-Back = N-back fMRI task; SST = Stop-Signal-Reaction-Time Task for fMRI; ALCUE = fMRI alcohol cue-reactivity task; MPRAGE = Magnetization Prepared - RApid Gradient Echo sequence; PANAS = Positive and Negative Affect Schedule; HSWBS = Habitual Subjective Well-Being Questionnaire; GSE = General Self-Efficacy Scale; Rosenberg = Rosenberg self-esteem scale; SWLS = Satisfaction with Life Scale; FSozU = Perceived Social Support Questionnaire; BDI-II = Beck-Depression Inventory; PSS = Perceived Stress Scale; STAI (X1,X2) = State / Trait Anxiety Inventory; ASRS-v1.1 = Adult ADHD Self-Report Scale Symptom Checklist, Part A; ADHS-SB = ADHD Self-rating Scale; BIS-15 = Barrett Impulsiveness Scale; COHS = Creature of Habit Scale; ACQ-SF-R = Alcohol Craving Questionnaire – short form revised; ADS = Alcohol Dependence Scale; AUQ = Alcohol Urge Questionnaire; CAS-A = Craving Automated Scale for Alcohol; OCDS-G = Obsessive Compulsive Drinking Scale - German; SRHI = Self-Report Habit Index (German translation, adapted for alcohol); VACS = Visual Analog Craving Scales for alcohol before and after fMRI for alcohol; OCSS = Obsessive Compulsive Smoking Scale; CAS-CS = Craving Automated Scale for Cigarette Smoking; QSU = Questionnaire on Smoking Urges; SCQ-A = Smoking Consequences Questionnaire for Adults; WSWS = Wisconsin Smoking Withdrawal Scale; SRHI = Self-Report Habit Index (tobacco); FTND = Fagerström Test for Nicotine Dependence; VACS = Visual Analog Craving Scales before and after fMRI for tobacco.

Figure captions

Figure 1: Study design. Following a screening, all participants will undergo a baseline (T1) appointment with diagnostic interviews, questionnaires, and functional magnetic resonance imaging measurements. Participants with tobacco or alcohol use disorder will be randomly assigned to the control group or intervention group. All participants will receive their respective treatment as usual. The intervention groups will additionally receive chess-based cognitive remediation training (CB-CRT). After the 6 week long treatment as usual with/ without CB-CRT (T2), the same measurements as for T1 will take place. During the follow-up period of 12 weeks, all participants will be contacted via telephone once a month.

Figure 2: Examples of the chess-based cognitive remediation training. 2a: Selective attention. Participants are asked to count the number of white knights on white squares (right answer: 5, squares: b1, b7, c6, d7, f1). During the training, participants receive 6 boards within a maximum of three minutes. **2b: Short term memory.** Participants are focused on the board and see the position for a few seconds up to one minute. Afterwards, the instructor asks the participants to reconstruct the position. Participants are asked to go to the front of the group and rebuild the position. 2**c: Executive functions, planification skills.** Participants must find out the shortest route the knight can go to capture the pawn. The knight must not stop on any square controlled by the rooks. The participant is asked to announce the number of moves before showing them on the board (correct answer: 4 moves – g5-e6-c7-b5-c3 or g5-e6-d4-b5-c3).

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Availability of data and materials

For protection of personal rights, and due to the sensitivity of the clinical and neuroimaging data, data will not be made publicly available. Upon direct request by other researchers and in mutual agreements (e.g., regarding data protection), anonymized data can be made available. Upon request, analysis procedures and codes will be shared with other researchers.

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Authors contributions

SVK designed the study. TW, GL, JH helped with designing the study. JAM developed the chess-based remediation training ECAM. GLX, JH, RS, AJR, DK, AW, SVK, SG adapted the training. SG, GL, and SVK wrote the manuscript. All authors read and approved the manuscript.

Conflicts of interest

All authors have no conflict of interest to declare.

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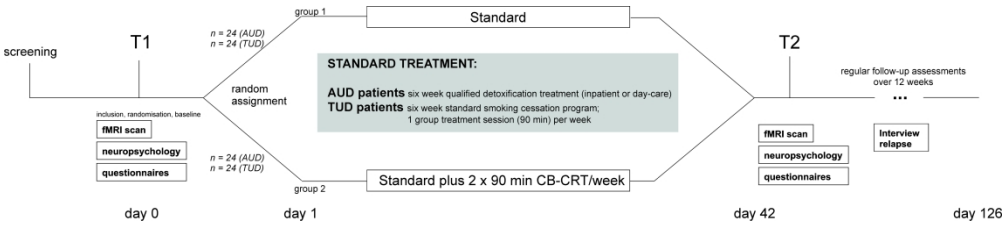

Figure 1: Study design.

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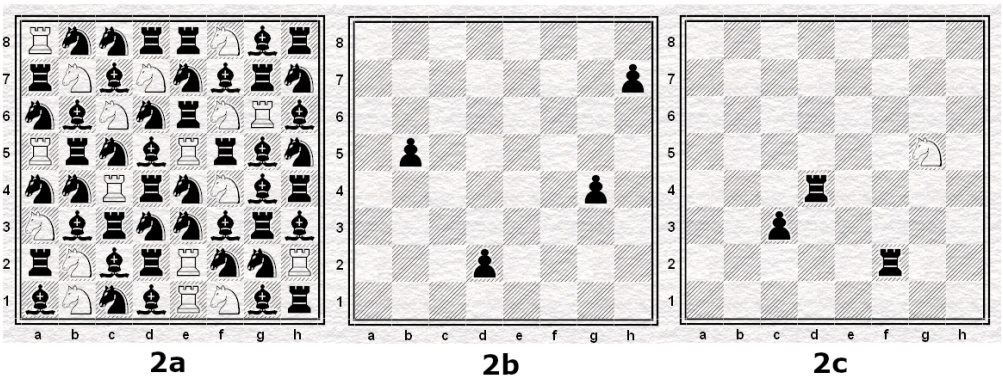

Figure 2: Examples of the chess-based cognitive remediation training.

98x38mm (300 x 300 DPI)

BMJ Open

Effects of chess-based cognitive remediation training as therapy add-on in alcohol and tobacco use disorders: protocol of a randomized, controlled fMRI study

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Effects of chess-based cognitive remediation training as therapy add-on in alcohol and tobacco use disorders: protocol of a randomized, controlled fMRI study

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Abstract

Background

Alcohol and tobacco use disorders (AUD, TUD) are frequent, both worldwide and in the German population, and cognitive impairments are known to facilitate instances of relapse. Cognitive training has been proposed for enhancing cognitive functioning and possibly improving treatment outcome in mental disorders. However, these effects and underlying neurobiological mechanisms are not yet fully understood regarding AUD and TUD. Examining the effect of chess-based cognitive remediation training (CB-CRT) on neurobiological, neuropsychological and psychosocial aspects as well as treatment outcomes will provide insights into mechanisms underlying relapse and abstinence and might help to improve health behaviour in affected individuals if used as therapy add-on.

Methods and Analysis

N=96 individuals with either AUD (N=48) or TUD (N=48) between the ages of 18 and 65 years will be randomized to four treatment groups. Two control groups will receive treatment as usual, i.e., AUD treatment in a clinic, TUD outpatient treatment. Two therapy add-on groups will receive a 6-week CB-CRT as a therapy add-on. functional magnetic resonance imaging (fMRI) tasks , neurocognitive tests will be administered before and afterwards. All individuals will be followed up on monthly for three months. Endpoints include alterations in neural activation and neuropsychological task performance, psychosocial functioning, and relapse or substance intake. Regarding fMRI analyses, a General Linear Model (GLM) will be applied and t-tests, full factorial models and regression analyses will be conducted on the second level. Behavioural and psychometric data will be analysed using t-tests, regression analyses, repeated-measures and one-way ANOVAs.

Ethics and Dissemination

This study has been approved by the ethics committee of the Medical Faculty Mannheim of the University of Heidelberg (2017-647N-MA). The findings of this study will be presented at conferences and published in peer-reviewed journals.

Trial registration

The study was registered in the Clinical Trials Register (trial identifier: NCT04057534 at clinicaltrials.gov).

Strengths and Limitations of this study

- The evaluation of the efficacy of CB-CRT as a supportive therapy add-on for SUD might lead to cost-efficient positive treatment outcomes.
- The use of objective measures to examine underlying neurobiopsychological mechanisms expands the current research on risk factors for relapse.
- The inclusion of two substances (alcohol and tobacco) increases the generalizability of the findings.
- The 6-week long therapy add-on might lead to drop-outs due to the large amount of time participants have to commit to the program.

Introduction

Substance use, including alcohol and tobacco use, is widespread both worldwide and in the German population. Worldwide, the prevalence for heavy episodic drinking of alcohol was estimated at 18.4% for adults, while daily smoking was estimated at 15.2%[1]. In 2018 in Germany, the prevalence of hazardous consumption of alcohol was estimated at 19.1%, and the 12-month prevalence for alcohol use disorder (AUD) at 5.9%. The prevalence of daily consumption of tobacco was estimated at 15.1%, and the 12-month prevalence for tobacco use disorder (TUD) at 8.6%[2]. In Germany, follow-up costs of alcohol use are estimated at 21 billion euros[3] and for tobacco use at 24 billion euros[4]. Furthermore, negative effects on health and on mortality rates are associated with TUD[5].

For individuals with AUD having undergone treatment, relapse rates between 22 and 86% have been observed during short-term follow-ups (16 weeks) up to a long-term follow-up of 16 years[6-8]. Following treatment, the relapse rate for TUD after one year is estimated to be between 2 and 17%[9]. A relapse can be brought on by heightened stress sensitivity, depressive mood, increased anxiety, or confrontation with a substance-related stimulus[10-12].

Even though some studies postulate intact, goal-directed behaviour in individuals with SUD [13-15], others observed neurobiological impairments in brain areas involved in inhibitory control in individuals with SUD[16-19]. In a model proposed by Bechara, SUD is viewed as an imbalance between two distinct, but closely interacting neural systems[20], which are essential for decision-making: The impulsive system is involved in the prediction and valuation of immediate rewards and includes such regions as the amygdala and the striatum. The reflective system signals long-term consequences of actions and involves the ventromedial prefrontal cortex (VMPFC), the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate, the insula, and the hippocampus. In SUD, it is assumed that the impulsive system becomes overactive, preventing the reflective system from exerting executive cognitive control over substance use. It might be those immediate rewards, such as pleasant effects derived from alcohol or nicotine consumption, are overvalued, and give preference over future rewards, such as health benefits associated with abstinence. Individuals with SUD also demonstrate a preference for smaller, immediate monetary rewards over larger, delayed ones[21]. Furthermore, the imbalance between impulsive and reflective systems reveals itself in dysfunctional inhibitory control, leading to increased risk taking[20]. Beyond these

impairments, individuals with SUD also demonstrate reduced cognitive functioning in the domains of problem solving, mental flexibility, forming judgments, and working memory[22]. A study using functional magnetic resonance imaging (fMRI)[23] found less activation in the right frontal cortex during a response inhibition task was associated with more cigarettes smoked in participants wanting to quit smoking. Other studies using fMRI have revealed a shift of neural activation from the ventral (nucleus accumbens) to the dorsal striatum (putamen and nucleus caudate), which was suggested to reflect a decrease in cortical control when viewing substance related cues [24]. Being related to executive functions, metacognitive abilities and beliefs play a major role in addiction[25]. In general, metacognition refers to the ability to know about cognition in general but, more importantly, to be aware of and know about one's own cognition[26]. Prefrontal regions, as well as the precuneus or dorsal anterior cingulate cortex seem to play an important role[27]. Generic and dysfunctional metacognitive beliefs, but also metacognitive beliefs about addiction-related thoughts or craving can predict the severity of addictive behaviour, craving, and relapse[25].

„Cognitive remediation" (Cognitive remediation therapy (CRT)) is a psychotherapeutic approach to improve cognitive deficits[28]. Cognitive training exercises span functional domains from executive functioning (inhibition, decision-making, cognitive flexibility, and working memory) to attention. Through repeated training, CRT can systematically stimulate and strengthen cognitive processes. A primary therapeutic objective is to improve the efficacy of other psychotherapeutic interventions, which require a minimal level of cognitive skill[29]. For example, it has been demonstrated that executive functioning skills can influence the efficacy of cognitive behavioural therapy[30]. CRT, specifically, has already been demonstrated to be successful as an add-on therapy in treating schizophrenia and eating disorders[31]. However, it has been suggested to explicitly teach metacognitive abilities in order to improve the outcome of CRT[32], since this might be a significant mechanism contributing to the effects of CRT in patients with schizophrenia[33]. Indeed, recent observations indicate a beneficial effect of CRT on metacognitive abilities, e.g., in schizophrenia[34]. As an add-on therapy to treat substance use disorders CRT seems promising[35] and cognitive training mostly results in improvements within the respective domains[36]. However, there is a lack of studies examining the efficacy of CRT as a modulator of cognition to improve treatment outcomes[37] and findings on the positive outcome following cognitive trainings in AUD are still mixed[38] or not present[39]. A review on

AUD[40] discussed that CRT improves split attention, recognition of warning signals, working memory, as well as episodic memory. Most relevantly, an improvement in working memory and inhibitory control was able to exert a positive influence on substance use patterns[40]. Additionally, including metacognitive trainings when treating individuals with SUD might be advantageous[25, 41].

Finally, promising studies have demonstrated a potential beneficial effect of classical chess training on the treatment of attention deficit hyperactivity disorder (ADHD) and schizophrenia as an add-on therapy. In the case of ADHD, classical chess training was able to effectively reduce disease severity[42]. A further study in patients with ADHD showed an improvement in the ability to concentrate[43]. Negative symptoms common to patients suffering from schizophrenia include a wide variety of cognitive deficits, including impaired attention-, memory-, learning- and problem-solving skills[44]. Chess training was able to rescue some of these deficits experienced by schizophrenic patients, improving voluntary processing, inhibitory capacity and planning proficiencies[45]. Examining the effects of chess training on mathematical problem-solving and metacognitive abilities in school children, no significant effects were observed compared to an active control group playing checkers and a passive control group[46].

Besides the known effects of CRT on metacognition, the beneficial effect of chess-based CRT still remains unclear. However, present findings suggest that chess-based CRT might be able to improve cognitive functioning in domains which can be improved by classical CRT, while simultaneously potentially improving specific domains modulated by chess-based interventions.

Consequently, our study aims to assess the effects of chess-based CRT (CB-CRT) on underlying neurobiological mechanisms of CB-CRT in AUD and TUD. We will use a novel and structured training program that, besides training cognitive functioning, includes metacognitive methods and social reinforcement. As a result of the comprehensiveness of the proposed study and the novel CB-CRT we will further assess the influence of CB-CRT on different aspects of cognition and psychosocial functioning as well as treatment outcome in individuals with AUD and TUD.

Method and Analyses

To investigate the effects of CB-CRT as a therapy add-on in alcohol and tobacco use disorders, N = 96 individuals will be examined. N = 48 AUD participants undergoing a qualified therapy or rehabilitation treatment for alcohol use disorder and N = 48 TUD participants who participate in a qualified smoking cessation group therapy will be included in the study. The Consolidated Standards Reporting Trials (CONSORT) statement was used for developing the study framework. Individuals with a diagnosis of AUD will be recruited from the out-patient and in-patient clinics of the Department of Addictive Behaviour and Addiction Medicine at the Central Institute of Mental Health and from the residential addiction treatment center MEDIAN Klinik Wilhelmsheim, Germany. Individuals with TUD will be recruited using public announcements including, flyers, and social media posts.

Half of each group (AUD, TUD) will be randomly assigned to either the control group or experimental group. Regarding the control groups, N = 24 AUD participants receive an in-patient qualified detoxification treatment program, an in- or out-patient rehabilitation program, or semi-inpatient therapy in a day-clinic. N = 24 TUD participants receive qualified smoking cessation group therapy following study inclusion. The out-patient smoking cessation therapy lasts for 6 weeks with one group therapy session à 1.5 hours per week. Individuals randomly allocated to the experimental group (24 individuals with AUD and 24 individuals with TUD) will receive CB-CRT for 1.5 hours twice a week for 6 weeks in addition to the standard treatment.

Patient and public involvement

Individuals currently or formerly affected by either AUD or TUD were involved in the development of the study design including outcome measurements. Two research colleagues with insight from both perspectives were consulted and supported the development and implementation of the study. The chess-based cognitive remediation training was utilized in practice as described in the following including patients with diverse mental disorders. It therefore grew in correspondence with the patients' feedback. In addition, a pilot study with patient from an addiction rehabilitation center resulted in good to very good patient ratings regarding helpfulness and acceptance. We will disseminate study results to interested patients. Also all study participants will always be able to discuss open questions throughout the process of the training with qualified research staff and they will receive feedback

regarding the goals of the training and study and the background of the methods used for training and study examination.

No patients are involved in the recruitment procedure and conduct of the study and the burden of study participation was not assessed beforehand by patients.

Examination procedure

Eligible participants between 18 and 65 years will be informed about the purpose and all aspects of the study. They will be provided with written study information according to the ethics regulations. Participants will be able to ask questions regarding the study. Afterwards, written informed consent will be obtained. All participants can withdraw their consent at any time. Then, study exclusion- and inclusion criteria will be examined. To do so, a structured clinical interview (SCID-5-CV)[47] will be performed to assess a possible history of lifetime and current mental disorders. Individuals with a diagnosis of severe mental or personality disorders will be excluded, e.g., lifetime bipolar disorder or schizophrenia or current severe depression, post-traumatic stress disorder. Current mild or moderate mental or personality disorders, such as mild anxiety-, adaptation, personality disorders or depression, will be tolerated. Individuals with AUD are included in the study after controlled abstinence for at least 72 hours, including completion of medically supervised detoxification (treatment of withdrawal symptoms with short-acting benzodiazepines or chlormethiazole must have been completed for at least three days). Individuals with TUD will be included following the intention to quit smoking. A detailed list of all inclusion and exclusion criteria regarding AUD and TUD are shown in table 1. Following study inclusion, participants will be randomly assigned to either the control or experimental group.

At the baseline examination appointment (T1) all participants will provide sociodemographic information and perform several neuropsychological tasks. An fMRI assessment will then take place. Participants will also fill out several questionnaires directly after the baseline assessment. After the 6 week long intervention period - either standard treatment alone or with CB-CRT as therapy add-on - a second examination appointment (T2) takes place. All participants will perform the same neuropsychological tasks again and the same fMRI assessment as conducted in T1 will take place. Participants will also fill out the same questionnaires as for T1. During a follow-up period of 12 weeks following the intervention, three telephone interviews (FU1, FU2, T3) will be conducted once a month. Instances of

relapse and amount of tobacco or alcohol consumption will be documented. Beyond this, the same questionnaires as for T1 and T2 will be completed.

Please see figure 1 for a detailed description of the study procedure and tables 2 and 3 for list of assessments used, including fMRI and neuropsychological paradigms, and questionnaires.

Standard Treatment

All study participants (TUD and AUD) will follow their respective treatment as usual (TAU). With regards to TUD, a qualified smoking cessation group therapy with one therapy session per week (90 minutes) will be held by a trained and certified psychologist. This intervention is strongly recommended in the latest version of the S3 guidelines for tobacco use disorder[48]. A superior effect on smoking cessation was observed following group therapy compared to, e.g., self-help or less intense interventions[49]. During the qualified smoking cessation group therapy, interventions following a cognitive-behavioural psychotherapy approach will be applied[50]. Study participants with AUD will follow the respective in-house or day-clinic therapeutic programme, as recommended by the respective S3 guidelines for alcohol use disorder[51]. This standard treatment includes medical and psychological interventions.

Chess-based cognitive remediation training

The planned CB-CRT „Entrenamiento cognitivo a través del ajedrez (ECAM, „Cognitive training through chess“, https://ajedrezmagic.es/el-entrenamiento-cognitivo-a-traves-del-ajedrez/) consists of a battery of tasks and was developed by one of the co-authors (J. A. M.). The training battery, which is administered in a group setting using mainly a chess demonstration board, is designed to strengthen cognitive functioning in specific domains such as selective attention (figure 2a), short-term memory (figure 2b), focal attention, pattern recognition, visuospatial abilities, planification skills (figure 2c), and inhibition. Participants do not need to know the game of chess. They will receive general information about the rules and strategies used for the corresponding training day. Overall, metacognitive abilities are trained as well, e.g., by giving psychoeducational information regarding different concepts of cognitive functioning, questioning, and identifying the underlying cognitive process, and enhancing the awareness of before mentioned aspects. Participants perform most of the specific tasks in front of the group and, for a social reinforcement effect, everyone will applaud the respective participant. Some of the tasks are conducted via paper-pencil. The training battery has been

utilized for more than ten years by J.A.M and his colleagues as an add-on therapy for elderly individuals, children with autism and/or ADHD, individuals with Down Syndrome, mental and other disorders, and in adults with SUD. The scientific evaluation of the program is one of the goals of the current study.

In an unpublished pilot study in the rehabilitation clinic at Comunidad Terapéutica La Garrovilla, N = 26 patients with SUD (N = 22 male; substances: alcohol, opiates, cocaine, benzodiazepines, cannabis) were examined. CB-CRT was applied in a group setting twice a week for a duration of 90 minutes each. Cognitive functioning, especially in executive functions, was assessed at admission to the clinic at Comunidad Terapéutica La Garrovilla, Badajoz (Extremadura, Spain) and again after 14 weeks. The neuropsychological testing battery included measures of general processing speed (trail-making test A), cognitive flexibility (trail-making test B)[52], planning abilities (Tower of London)[53] and intelligence (Wechsler Adult Intelligence Scale, WAIS). Significant increases in performance were found after 14 weeks of treatment in general processing speed (trail-making test A; p = .001), cognitive flexibility (trail-making test B; p = .013), the Tower of London test (p = .001) as well as in the WAIS measures for verbal comprehension (“similarities”, p = .019) and for working memory (“letter-number sequencing”, p = .030, “digit span forward”, p = .044, “digit span backward”, p = .018, “digit span total”, p = .007). Performance in the WAIS measures “coding” (processing speed) and “matrix reasoning” (perceptual reasoning) did not differ significantly. In another sample of N = 15 patients receiving the chess-based add-on treatment for 3.5 months, subjective satisfaction was evaluated. On scales ranging from 1 (very unsatisfied / very poor) to 4 (very satisfied / very good), 73% of the patients rated the overall program as very good (i. e. score of 4). 67% of the patients found the program very helpful in treating their SUD (score of 4), 27% found it helpful (score of 3). Further, when asked how the program influenced other domains being negatively affected by SUD before admission, 53% found the program very supportive (score of 4), 27% found it supportive (score of 3). Besides this, 87% reported that the program helped them to increase their memory capabilities, 93% stated a subjective increase in attention performance, and 93% reported an enhancement in decision-making.

Self-rating Questionnaires

Self-rating questionnaires will be administered to address factors related to, e.g., impulsiveness and inhibitory control, mood, psychosocial functioning, as well as substance consumption, or craving. Please see Table 2 for a detailed list.

Neuropsychological assessments

Tasks investigating components of working memory (Wechsler Memory Scale-3)[54], decision-making (Iowa Gambling Task)[55], as well as mental flexibility (Dimensional Change Card Sort)[56] and attentional capacity (d2-R Test of Attention)[57] will be administered.

fMRI assessments

During the fMRI scanner examination, study participants will perform a stop-signal task[58], alcohol- and tobacco based cue-reactivity tasks[59, 60], an N-back task[61] and a resting-state MRI. Scanning will be performed with a 3T whole-body tomograph (MAGNETOM Prisma; Siemens, Erlangen, Germany). T2* weighted multi-band echo-planar images (mb-EPI) using a multi-band acceleration factor 6 will be acquired in a transversal orientation 20° clockwise to AC-PC-line covering the whole brain (TR = 869 ms, TE = 38 ms, 60 slices, slice thickness = 2.4 mm, voxel size 2.4 × 2.4 × 2.4 mm, no inter-slice gap, field of view (FoV) = 210 mm, matrix size 88 x 88, acquisition orientation T > C, interleaved slice order, acceleration factor slice = 6, flip angle = 58°, bandwidth = 1832 Hz/Px, prescan normalize, weak raw data filter, LeakBlock kernel, fat sat). This short TE and the 20° flip to AC-PC orientation is chosen to minimize susceptibility artefacts. Scanner sequences are provided by the Center for Magnetic Resonance Research (CMRR), University of Minnesota, Minneapolis, MN, USA (https://www.cmrr.umn.edu/multiband/)[62]. In addition, a T1-weighted 3D MPRAGE (Magnetization Prepared - RApid Gradient Echo) dataset consisting of 208 sagittal slices (slice thickness 1 mm, 1×1×1 mm voxel size, FOV 256 x 256 mm^2, TR= 2000ms, TE = 2.01 ms, TI = 800 ms, flip angle = 8°) will be acquired.

Endpoints

endpoints are changes in neural alcohol and tobacco cue-reactivity[59, 60] (e.g., reduction in substance-related activation of striatal brain regions), neural correlates of inhibition (stop-signal task)[63] (e.g., increased dorsolateral prefrontal neural activation) and working memory (N-back task)[61] (e.g., increased inferior frontal neural activation), as well as functional

connectivity within the salience network (SN; insula, anterior cingulate cortex) and executive control network (ECN; dorsolateral frontal and lateral posterior parietal cortices) using resting-state fMRI data. Also, working memory capacity (letter-number sequencing task of the Wechsler Memory Scale-3)[54], impulsivity (Barratt Impulsiveness Scale-15)[64, 65], mental flexibility (Dimensional Change Card Sort)[56], decision-making (Iowa Gambling Task)[55, 66] and attentional capacity (d2-R Test of Attention)[67], summarized as cognitive functioning, are endpoints of interest. Additionally, the duration until the first severe relapse (daily smoking of at least one cigarette at day, consumption of more than 48 grams (females) or 60 grams (males) of alcohol) during the follow-up periods and amount of substance consumption in case of a relapse as well as improvements in psychosocial functioning will be examined.

Sample size calculation

Using the software package G*Power[68] the sample size calculation was conducted for the main primary outcomes, i.e., neurobiological correlates underlying adaptations following the CB-CRT, where we expected a minimum effect size of f = 0.2 for all constructs (ANOVA with repeated measures, within- and between subject factors and interactions). In this case, ideal sample coverage would be 24 individuals per group (at 80% power, alpha-level 5%).

Data analysis plan

To analyse psychometric and neuropsychological data, SPSS (Statistics for Windows, Version 25.0. IBM Corp., Armonk, NY) will be used. The various dependent variables will be evaluated using multivariate analyses of variance with repeated measures. To counteract possible group differences at baseline, a percentage in change (divide by T1 values) or variable values at T1 can be incorporated in subsequent statistical analyses as a covariate. In addition, linear regression models will be calculated to examine the influence of confounding variables (for example, severity of tobacco or alcohol dependence) on the observed change in dependent variables as described previously (e.g., craving, task performance, psychosocial well-being). Cox-regression analyses, including, e.g., brain activation in the dorsolateral prefrontal or inferior frontal regions during inhibition and executive functioning, or the ventral striatum during cue reactivity tasks as predictors, will be conducted to examine the association with relapse. To analyse the fMRI data, SPM12 (Wellcome Department of Cognitive Neurology, London, UK) running under Matlab will be used. The pre-processing pipeline will include

motion correction, normalization to the Montreal Neurological Institute (MNI) template, and a spatial smoothing with Gaussian kernel of 8 mm full width at half maximum (FWHM) will be conducted. The pre-processed data will then be used for first- and second-level analyses. On the first level (within-subject), neural activation associated with task conditions (contrasts) will be modelled via a convolution with a canonical hemodynamic response function (HFR) following a general linear model (GLM). A high-pass filter to remove low-frequency components of fMRI time-series will be used. Depending on the fMRI tasks, specific contrasts regarding task conditions will be modelled as described in the above cited literature. On the second level (between-subject) and regarding the effects of group and time, paired t-tests (e.g., pre vs. post intervention within one group) and full factorial models will be used. Additionally, regression models including clinical variables, such as severity of TUD or AUD, will be calculated. To control for multiple statistical testing, we will use established correction procedures, e.g., whole brain family-wise error correction (FWE) for fMRI analyses or Bonferroni correction for other statistical analyses.

Hypotheses

Primary hypotheses

1. CB-CRT improves aberrant neural alcohol cue-reactivity (measured by alcohol and tobacco cue-reactivity fMRI tasks) in AUD/TUD in comparison to standard treatment alone
2. CB-CRT improves neuronal aberrations present when executing cognitive tasks (measured by N-back and stop-signal fMRI task) in individuals with AUD/TUD in comparison to standard treatment alone.
3. CB-CRT decreases functional connectivity within the salience network in individuals with AUD/TUD in comparison to standard treatment alone.
4. CB-CRT decreases functional connectivity within the executive control network in individuals with AUD/TUD in comparison to standard treatment alone.
5. CB-CRT improves cognitive functioning (measured by neuropsychological tasks) in AUD/TUD individuals in comparison to standard treatment alone.
6. CB-CRT improves psychosocial functioning (measured by, e.g., HSWBS, SWLS) in AUD/TUD individuals in comparison to standard treatment alone. CB-CRT influences

the treatment process, e.g., time to first severe relapse, for AUD/TUD individuals positively in comparison to standard treatment alone.

Secondary hypotheses

1. CB-CRT might be more efficacious in individuals with impaired cognitive functioning, low self-esteem, self-efficacy, and social support.
2. Chess as a three-week add-on therapy influences the treatment process, e.g., time to first severe relapse for AUD/TUD individuals moderated and mediated by cognitive, affective, and psychosocial factors.

Discussion

The here presented study aims to examine the effect of CB-CRT as treatment add-on on neurobiological processes but also neuropsychological and psychosocial functioning known to contribute to the development and maintenance of AUD and TUD. The effect of CB-CRT might also results in longer times of abstinence or reduced substance consumption. If CB-CRT as therapy add-on, as examined in this comprehensive study, shows to be more effective than standard treatment alone, this intervention might help to improve health behaviour in affected individuals.

Limitations with respect to the interpretability of the data might derive from the study design. We aim to examine the superior effect of CB-CRT compared to treatment as usual in therapy outcomes that might rely on neurobiological alterations following this training. As postulated by Sala and Gobet (69) a third, active control group might be needed to ultimately evaluate the chess-specific mechanisms and outcomes. Therefore and in case of successfully demonstrating a superior effect of our CB-CRT, a subsequent study might be needed to address this question. Further, even in light of our future results confirming a superior effect of CB-CRT as therapy add-on on neurobiological and neuropsychological processes, these improvements might to translate to longer abstinence or a reduction in the amount of substance consumption. Previously, this has been demonstrated in AUD: Even though an improvement in working memory functioning has been observed following an active working-memory training in patients with AUD, heavy drinking and neuropsychological functioning in other domains remained unchanged[39].

Since the described study includes a cognitive remediation training that exceeds merely training individual domains, we hope to counteract limitations of previous studies. Including

social (training in the group) and metacognitive aspects, the CB-CRT might generalize from altering neurobiological processing to behavioural changes, i.e. substance consumption.

Ethics and dissemination

The study was approved by the local Ethics Committee of the Medical Faculty Mannheim at the University of Heidelberg, Germany (reference number 2017-647N-MA). Before study inclusion and after a detailed explanation of all procedures, all participants will provide written informed consent. The study was registered in the Clinical Trials Register (trial identifier: NCT04057534) on December 8th, 2019. The study results will be disseminated by peer-review publications and conference presentations. Open-access publication is planned for all peer-reviewed publications. All participants are offered to receive a print of the final, published version of peer-reviewed publications. For protection of personal rights, and due to the sensitivity of the clinical and neuroimaging data, data will not be made publicly available. Upon direct request by other researchers and in mutual agreements (e.g., regarding data protection), anonymized data can be made available. Upon request, analysis procedures and codes will be shared with other researchers.

Risks associated with participation

Participants will be asked several questions regarding their substance consumption, mood, quality of life. They will additionally perform neuropsychological and fMRI tasks. Both excerpts a strain on the participants in terms of time and effort. Further, it may cause emotional discomfort in some participants. To counteract these possible negative consequences of study participations, the research team, also consisting of psychologists and psychotherapists in training, will regularly check if participants and evaluate their (dis)comfort. Contact to qualified clinicians will be made possible in case of severe emotional discomfort. Due to the length of the study appointments, we will offer participants the option to flexibly answer most of the questionnaires at home.

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Availability of data and materials

For protection of personal rights, and due to the sensitivity of the clinical and neuroimaging data, data will not be made publicly available. Upon direct request by other researchers and in mutual agreements (e.g., regarding data protection), anonymized data can be made available. Upon request, analysis procedures and codes will be shared with other researchers.

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Authors contributions

SVK designed the study. TW, GL, JH helped with designing the study. JAM developed the chess-based remediation training ECAM. GL, JH, RS, AJR, DK, AW, SVK, SG adapted the training. SG, GL, and SVK wrote the manuscript. All authors read and approved the manuscript.

Conflicts of interest

All authors have no conflict of interest to declare.

Tables

Table 1: Inclusion and exclusion criteria of the overall study sample. Specific criteria for AUD and TUD are highlighted.

Inclusion criteria	Exclusion criteria
• Age between 18 and 65 years • Normal or corrected to normal vision • Signed written informed consent • Signed consent for data security	• Pregnancy • Positive alcohol test • Common exclusion criteria for MRI (e.g., metal, claustrophobia, epilepsy, adiposity) • Suicidality • Severe cognitive impairments (e.g., dementia) • Severe physical illness • Neurological disorders, history of brain injury • Therapy with methylphenidate within the last 8 weeks • Other mental disorders, except for mild or moderate anxiety-, adaptation-, post-traumatic stress-, personality-, attention deficit / hyperactivity disorders

AUD	TUD	AUD	TUD
• AUD according to DSM-5 (more than 3 fulfilled criteria) • Currently in therapy for AUD (in-patient or outpatient therapy) • Abstinence from alcohol > 72h	• TUD according to DSM-5 (more than 3 fulfilled criteria) • Participation in smoking cessation therapy	• Other Axis I mental disorder except for mild, moderate or remitted depression, other substance use disorders if AUD is still the main diagnosis • Severe withdrawal symptoms (CIWA-Ar > 7; Sullivan et al. 1989) • Psychotropic medication within the last 14 days except for antidepressants or soporific and intake of medication for treating withdrawal effects until 3 days prior to study participation	• Other Axis I mental disorder except for mild or remitted depression, other mild substance use disorders (i.e., max. of 3 fulfilled DSM-5 criteria in the last 12 months) • Psychotropic medication within the last 14 days except for antidepressants

Note: AUD = Alcohol use disorder; TUD = Tobacco use disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders; MRI = Magnetic resonance imaging

Table 2: Self-rating questionnaires.

Questionnaire	Short term	Measurement Aim	Reference
Goal attainment scale	GAS	Abstinence-related goals	[70]
Rosenberg Scale		Self-esteem	[71]
General Self-Efficacy Scale	GSE	Self-efficacy	[72]
Perceived Social Support Questionnaire	F-SozU	Perceived social support	[73]
Habitual Subjective Well-Being Questionnaire	SWLS	Psychological well-being	[74]
Satisfaction with Life Scale	SWLS	Life satisfaction	[75]
Positive and Negative Affect Schedule	PANAS	Affect	[76]
State-Trait Anxiety Inventory		Anxiety	[77]
	STAI X2	Personality trait	
	STAI X1	Temporary state	
Beck Depression Inventory II	BDI II	Depression	[78, 79]
Percived Stress Scale	PSS	Perceived stress	[80]
Barratt Impulsiveness Scale	BIS-15	Impulsivity	[64, 65]
Adult ADHD Self-Report Scale-V1.1 Symptoms Checklist	ASRS-V1.1	ADHD symptoms	[81]
ADHD Self-Rating Scale	ADHD-SB	ADHD symptoms	[82]
Creature of Habit Scale	COHS	Automatic behaviour	[83]
Self-Report Habit Index	SRHI	Substance-related habits	[84]
Fagerström Test for Nicotine Dependence	FTND	Intensity of physical nicotine dependence	[85]
Alcohol Use Disorder Identification Test	AUDIT	Screening for alcohol use disorder	[86]
Clinical Institute Withdrawal Assessment for Alcohol	CIWA-Ar	Alcohol withdrawal symptoms	[87]
Form90		Alcohol or nicotine consumption	[88]
Visual Analog Craving Scales	VACS	Alcohol or nicotine craving	[89]
Obsessive Compulsive Drinking Scale	OCDS-G	Thoughts about alcohol and drinking behaviour	[90]
Alcohol Craving Questionnaire	ACQ-SF-R	Acute alcohol craving	[91]
Craving Automated Scale for Alcohol	CAS-A	Alcohol craving and automated drinking behaviour	[92]
Alcohol Urge Questionnaire	AUQ	Alcohol urges	[93]
Alcohol Dependence Scale	ADS	Severity of alcohol dependence	[94]
Questionnaire on Smoking Urges	QSU	Smoking urges	[95]
Craving Automated Scale for Cigarette Smoking	CAS-CS	Nicotine craving and automated smoking behaviour	[60]
Obsessive Compulsive Smoking Scale	OCSS	Thoughts about tobacco and smoking behaviour	[96]
Smoking Consequences Questionnaire for Adults	SCQ-A	Smoking outcome expectancies	[97]
Wisconsin Smoking Withdrawal Scale	WSWS	Nicotine withdrawal symptoms	[98]

Note: ADHD = Attention Deficit Hyperactivity Disorder.

Table 3: Schedule of measurement during study participation.

Measurement time point	**S**		**T1**		**T2**		**FU1**		**FU2**		**T3**	
Baseline	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
Demographic information	x	x	x	x								
Current medication*	x	x	x	x	x	x					x	x
Current somatic or mental conditions*	x	x	x	x	x	x					x	x
Structured Clinical Interview (SCID-5-CV)			x	x								
Smoking history			x	x								
Current smoking behavior*					x		x		x		x	x
Smoking Assessment Interview			x		x						x	
(Current) drinking behavior*		x		x		x		x		x	x	x
CIWA-Ar				x		x						
Current drug use*	x	x									x	x
Urine pregnancy and drugs screening			x	x	x	x						
Breath alcohol test			x	x	x	x						
Breath carbon monoxide test			x		x							
Goal attainment scaling			x	x	x	x						
Neuropsychology	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
MWT-B			x									
LNS-Task			x		x							
D2-R			x	x	x	x						
IGT			x	x	x	x						
DCCS			x	x	x	x						
Magnetic resonance imaging	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
Field-Map			x	x	x	x						
Resting-State			x	x	x	x						
NICUETINE			x	x	x	x						
N-Back			x	x	x	x						
SST			x	x	x	x						
ALCUE			x	x	x	x						
MPRAGE			x	x	x	x						
General questionnaires	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
PANAS			x	x	x	x	x	x	x	x	x	x
HSWBS			x	x	x	x						
GSE			x	x								
Rosenberg			x	x								
SWLS			x	x	x	x					x	x
FSozU			x	x								
Questionnaires - depression and anxiety	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
BDI II			x	x	x	x					x	x
PSS			x	x	x	x					x	x
STAI (X1)			x	x	x	x					x	x
STAI (X2)			x	x								
Questionnaires – impulsivity and ADHD	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
ASRS-v1.1			x	x	x	x						
ADHS-SB			x		x							
BIS-15			x	x	x	x					x	x
COHS			x	x								
Questionnaires - alcohol	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
ACQ-SF-R				x		x						x
ADS				x								
AUDIT	x	x										
AUQ				x		x		x		x		
CAS-A				x		x						x

OCDS-G				x		x		x		x		x		
SRHI (alcohol)				x		x						x		
VACS for MRI (alcohol)			x	x	x	x								
Questionnaires - tobacco	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
OCSS			x		x		x		x		x			
CAS-CS			x	x	x						x			
QSU			x		x		x		x		x			
SCQ-A			x		x						x			
WSWS			x		x						x			
SRHI (tobacco)			x		x						x			
FTND			x	x	x						x			
VACS for MRI (tobacco)			x		x									

Note: S = Screening measurement, T1 = baseline and MRI assessment, T2 = MRI assessment, FU = monthly follow-ups via telephone; T3 = final follow-up via telephone; T = Tobacco use disorder; A = Alcohol use disorder; * self-report.

SCID = Structured Clinical Interview for DSM-5; AUDIT = Alcohol Use Disorder Identification Test; CIWA-AR = Clinical Institute Withdrawal Assessment; MWT-B = Multiple-choice vocabulary test (German version); LNS = Letter-Number-Sequencing (Wechsler-Memory Scale-3); D2-R = d2-R Test of Attention; IGT = Iowa Gambling Task; DCCS = Dimensional Change Card Sort; NICUETINE = fMRI tobacco cue-reactivity task; N-Back = N-back fMRI task; SST = Stop-Signal-Reaction-Time Task for fMRI; ALCUE = fMRI alcohol cue-reactivity task; MPRAGE = Magnetization Prepared - RApid Gradient Echo sequence; PANAS = Positive and Negative Affect Schedule; HSWBS = Habitual Subjective Well-Being Questionnaire; GSE = General Self-Efficacy Scale; Rosenberg = Rosenberg self-esteem scale; SWLS = Satisfaction with Life Scale; FSozU = Perceived Social Support Questionnaire; BDI-II = Beck-Depression Inventory; PSS = Perceived Stress Scale; STAI (X1,X2) = State / Trait Anxiety Inventory; ASRS-v1.1 = Adult ADHD Self-Report Scale Symptom Checklist, Part A; ADHS-SB = ADHD Self-rating Scale; BIS-15 = Barrett Impulsiveness Scale; COHS = Creature of Habit Scale; ACQ-SF-R = Alcohol Craving Questionnaire – short form revised; ADS = Alcohol Dependence Scale; AUQ = Alcohol Urge Questionnaire; CAS-A = Craving Automated Scale for Alcohol; OCDS-G = Obsessive Compulsive Drinking Scale - German; SRHI = Self-Report Habit Index (German translation, adapted for alcohol); VACS = Visual Analog Craving Scales for alcohol before and after fMRI for alcohol; OCSS = Obsessive Compulsive Smoking Scale; CAS-CS = Craving Automated Scale for Cigarette Smoking; QSU = Questionnaire on Smoking Urges; SCQ-A = Smoking Consequences Questionnaire for Adults; WSWS = Wisconsin Smoking Withdrawal Scale; SRHI = Self-Report Habit Index (tobacco); FTND = Fagerström Test for Nicotine Dependence; VACS = Visual Analog Craving Scales before and after fMRI for tobacco.

Figure captions

Figure 1: Study design. Following a screening, all participants will undergo a baseline (T1) appointment with diagnostic interviews, questionnaires, and functional magnetic resonance imaging measurements. Participants with tobacco or alcohol use disorder will be randomly assigned to the control group or intervention group. All participants will receive their respective treatment as usual. The intervention groups will additionally receive chess-based cognitive remediation training (CB-CRT). After the 6 week long treatment as usual with/ without CB-CRT (T2), the same measurements as for T1 will take place. During the follow-up period of 12 weeks, all participants will be contacted via telephone once a month.

Figure 2: Examples of the chess-based cognitive remediation training. 2a: Selective attention. Participants are asked to count the number of white knights on white squares (right answer: 5, squares: b1, b7, c6, d7, f1). During the training, participants receive 6 boards within a maximum of three minutes. **2b: Short term memory.** Participants are focused on the board and see the position for a few seconds up to one minute. Afterwards, the instructor asks the participants to reconstruct the position. Participants are asked to go to the front of the group and rebuild the position. 2**c: Executive functions, planification skills.** Participants must find out the shortest route the knight can go to capture the pawn. The knight must not stop on any square controlled by the rooks. The participant is asked to announce the number of moves before showing them on the board (correct answer: 4 moves – g5-e6-c7-b5-c3 or g5-e6-d4-b5-c3).

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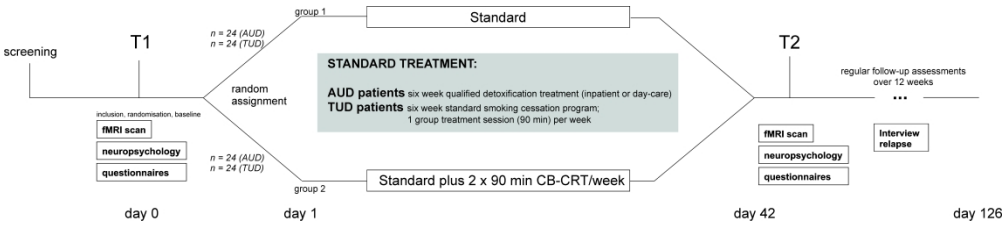

Figure 1: Study design.

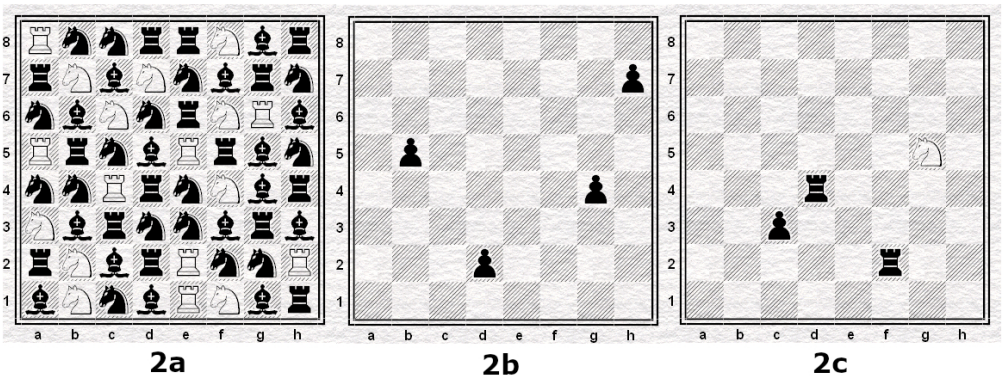

Figure 2: Examples of the chess-based cognitive remediation training.

98x38mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	p.1-2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	p.4-6	Explain the scientific background and rationale for the investigation being reported
Objectives	p.6; 13-14	State specific objectives, including any prespecified hypotheses
Methods		
Study design	p.7	Present key elements of study design early in the paper
Setting	p. 7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	p.8-9	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case
Variables	p.8-11	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	p.8-11	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	n/a	Describe any efforts to address potential sources of bias
Study size	p. 12	Explain how the study size was arrived at
Quantitative variables	n/a	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	p. 12-13	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how matching of cases and controls was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	n/a	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	n/a	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	n/a	Report numbers in each exposure category, or summary measures of exposure
Main results	n/a	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	n/a	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	n/a	Summarise key results with reference to study objectives
Limitations	p.14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	n/a	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	n/a	Discuss the generalisability (external validity) of the study results
Other information		
Funding	p.15-16	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Effects of chess-based cognitive remediation training as therapy add-on in alcohol and tobacco use disorders: protocol of a randomized, controlled clinical fMRI trial

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Abstract

Background

Alcohol and tobacco use disorders (AUD, TUD) are frequent, both worldwide and in the German population, and cognitive impairments are known to facilitate instances of relapse. Cognitive training has been proposed for enhancing cognitive functioning and possibly improving treatment outcome in mental disorders. However, these effects and underlying neurobiological mechanisms are not yet fully understood regarding AUD and TUD. Examining the effect of chess-based cognitive remediation training (CB-CRT) on neurobiological, neuropsychological and psychosocial aspects as well as treatment outcomes will provide insights into mechanisms underlying relapse and abstinence and might help to improve health behaviour in affected individuals if used as therapy add-on.

Methods and Analysis

N=96 individuals with either AUD (N=48) or TUD (N=48) between 18 and 65 years of age will participate in a randomized, controlled clinical fMRI trial. Two control groups will receive treatment as usual, i.e., AUD treatment in a clinic, TUD outpatient treatment. Two therapy add-on groups will receive a 6-week CB-CRT as a therapy add-on. Functional magnetic resonance imaging (fMRI) tasks, neurocognitive tests will be administered before and afterwards. All individuals will be followed up on monthly for three months. Endpoints include alterations in neural activation and neuropsychological task performance, psychosocial functioning, and relapse or substance intake. Regarding fMRI analyses, a General Linear Model (GLM) will be applied and t-tests, full factorial models and regression analyses will be conducted on the second level. Behavioural and psychometric data will be analysed using t-tests, regression analyses, repeated-measures and one-way ANOVAs.

Ethics and Dissemination

This study has been approved by the ethics committee of the Medical Faculty Mannheim of the University of Heidelberg (2017-647N-MA). The findings of this study will be presented at conferences and published in peer-reviewed journals.

Trial registration

The study was registered in the Clinical Trials Register (trial identifier: NCT04057534 at clinicaltrials.gov).

Strengths and Limitations of this study

- The evaluation of the efficacy of CB-CRT as a supportive therapy add-on for SUD might lead to cost-efficient positive treatment outcomes.
- The use of objective measures to examine underlying neurobiopsychological mechanisms expands the current research on risk factors for relapse.
- The inclusion of two substances (alcohol and tobacco) increases the generalizability of the findings.
- The 6-week long therapy add-on might lead to drop-outs due to the large amount of time participants have to commit to the program.

Introduction

Substance use, including alcohol and tobacco use, is widespread both worldwide and in the German population. Worldwide, the prevalence for heavy episodic drinking of alcohol was estimated at 18.4% for adults, while daily smoking was estimated at 15.2%[1]. In 2018 in Germany, the prevalence of hazardous consumption of alcohol was estimated at 19.1%, and the 12-month prevalence for alcohol use disorder (AUD) at 5.9%. The prevalence of daily consumption of tobacco was estimated at 15.1%, and the 12-month prevalence for tobacco use disorder (TUD) at 8.6%[2]. In Germany, follow-up costs of alcohol use are estimated at 21 billion euros[3] and for tobacco use at 24 billion euros[4]. Furthermore, negative effects on health and on mortality rates are associated with TUD[5].

For individuals with AUD having undergone treatment, relapse rates between 22 and 86% have been observed during short-term follow-ups (16 weeks) up to a long-term follow-up of 16 years[6-8]. Following treatment, the relapse rate for TUD after one year is estimated to be between 2 and 17%[9]. A relapse can be brought on by heightened stress sensitivity, depressive mood, increased anxiety, or confrontation with a substance-related stimulus[10-12].

Even though some studies postulate intact, goal-directed behaviour in individuals with SUD [13-15], others observed neurobiological impairments in brain areas involved in inhibitory control in individuals with SUD[16-19]. In a model proposed by Bechara, SUD is viewed as an imbalance between two distinct, but closely interacting neural systems[20], which are essential for decision-making: The impulsive system is involved in the prediction and valuation of immediate rewards and includes such regions as the amygdala and the striatum. The reflective system signals long-term consequences of actions and involves the ventromedial prefrontal cortex (VMPFC), the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate, the insula, and the hippocampus. In SUD, it is assumed that the impulsive system becomes overactive, preventing the reflective system from exerting executive cognitive control over substance use. It might be those immediate rewards, such as pleasant effects derived from alcohol or nicotine consumption, are overvalued, and give preference over future rewards, such as health benefits associated with abstinence. Individuals with SUD also demonstrate a preference for smaller, immediate monetary rewards over larger, delayed ones[21]. Furthermore, the imbalance between impulsive and reflective systems reveals itself in dysfunctional inhibitory control, leading to increased risk taking[20]. Beyond these

impairments, individuals with SUD also demonstrate reduced cognitive functioning in the domains of problem solving, mental flexibility, forming judgments, and working memory[22]. A study using functional magnetic resonance imaging (fMRI)[23] found less activation in the right frontal cortex during a response inhibition task was associated with more cigarettes smoked in participants wanting to quit smoking. Other studies using fMRI have revealed a shift of neural activation from the ventral (nucleus accumbens) to the dorsal striatum (putamen and nucleus caudate), which was suggested to reflect a decrease in cortical control when viewing substance related cues [24]. Being related to executive functions, metacognitive abilities and beliefs play a major role in addiction[25]. In general, metacognition refers to the ability to know about cognition in general but, more importantly, to be aware of and know about one's own cognition[26]. Prefrontal regions, as well as the precuneus or dorsal anterior cingulate cortex seem to play an important role[27]. Generic and dysfunctional metacognitive beliefs, but also metacognitive beliefs about addiction-related thoughts or craving can predict the severity of addictive behaviour, craving, and relapse[25].

„Cognitive remediation" (Cognitive remediation therapy (CRT)) is a psychotherapeutic approach to improve cognitive deficits[28]. Cognitive training exercises span functional domains from executive functioning (inhibition, decision-making, cognitive flexibility, and working memory) to attention. Through repeated training, CRT can systematically stimulate and strengthen cognitive processes. A primary therapeutic objective is to improve the efficacy of other psychotherapeutic interventions, which require a minimal level of cognitive skill[29]. For example, it has been demonstrated that executive functioning skills can influence the efficacy of cognitive behavioural therapy[30]. CRT, specifically, has already been demonstrated to be successful as an add-on therapy in treating schizophrenia and eating disorders[31]. However, it has been suggested to explicitly teach metacognitive abilities in order to improve the outcome of CRT[32], since this might be a significant mechanism contributing to the effects of CRT in patients with schizophrenia[33]. Indeed, recent observations indicate a beneficial effect of CRT on metacognitive abilities, e.g., in schizophrenia[34]. As an add-on therapy to treat substance use disorders CRT seems promising[35] and cognitive training mostly results in improvements within the respective domains[36]. However, there is a lack of studies examining the efficacy of CRT as a modulator of cognition to improve treatment outcomes[37] and findings on the positive outcome following cognitive trainings in AUD are still mixed[38] or not present[39]. A review on

AUD[40] discussed that CRT improves split attention, recognition of warning signals, working memory, as well as episodic memory. Most relevantly, an improvement in working memory and inhibitory control was able to exert a positive influence on substance use patterns[40]. Additionally, including metacognitive trainings when treating individuals with SUD might be advantageous[25, 41].

Finally, promising studies have demonstrated a potential beneficial effect of classical chess training on the treatment of attention deficit hyperactivity disorder (ADHD) and schizophrenia as an add-on therapy. In the case of ADHD, classical chess training was able to effectively reduce disease severity[42]. A further study in patients with ADHD showed an improvement in the ability to concentrate[43]. Negative symptoms common to patients suffering from schizophrenia include a wide variety of cognitive deficits, including impaired attention-, memory-, learning- and problem-solving skills[44]. Chess training was able to rescue some of these deficits experienced by schizophrenic patients, improving voluntary processing, inhibitory capacity and planning proficiencies[45]. Examining the effects of chess training on mathematical problem-solving and metacognitive abilities in school children, no significant effects were observed compared to an active control group playing checkers and a passive control group[46].

Besides the known effects of CRT on metacognition, the beneficial effect of chess-based CRT still remains unclear. However, present findings suggest that chess-based CRT might be able to improve cognitive functioning in domains which can be improved by classical CRT, while simultaneously potentially improving specific domains modulated by chess-based interventions.

Consequently, our study aims to assess the effects of chess-based CRT (CB-CRT) on underlying neurobiological mechanisms of CB-CRT in AUD and TUD. We will use a novel and structured training program that, besides training cognitive functioning, includes metacognitive methods and social reinforcement. As a result of the comprehensiveness of the proposed study and the novel CB-CRT we will further assess the influence of CB-CRT on different aspects of cognition and psychosocial functioning as well as treatment outcome in individuals with AUD and TUD.

Method and Analyses

To investigate the effects of CB-CRT as a therapy add-on in alcohol and tobacco use disorders, N = 96 individuals will be examined in a randomized, controlled clinical fMRI trial. N = 48 AUD participants undergoing a qualified therapy or rehabilitation treatment for alcohol use disorder and N = 48 TUD participants who participate in a qualified smoking cessation group therapy will be included in the study. The Consolidated Standards Reporting Trials (CONSORT) statement was used for developing the study framework. Individuals with a diagnosis of AUD will be recruited from the out-patient and in-patient clinics of the Department of Addictive Behaviour and Addiction Medicine at the Central Institute of Mental Health and from the residential addiction treatment center MEDIAN Klinik Wilhelmsheim, Germany. Individuals with TUD will be recruited using public announcements including, flyers, and social media posts.

Half of each group (AUD, TUD) will be randomly assigned to either the control group or experimental group. Regarding the control groups, N = 24 AUD participants receive an in-patient qualified detoxification treatment program, an in- or out-patient rehabilitation program, or semi-inpatient therapy in a day-clinic. N = 24 TUD participants receive qualified smoking cessation group therapy following study inclusion. The out-patient smoking cessation therapy lasts for 6 weeks with one group therapy session à 1.5 hours per week. Individuals randomly allocated to the experimental group (24 individuals with AUD and 24 individuals with TUD) will receive CB-CRT for 1.5 hours twice a week for 6 weeks in addition to the standard treatment.

Patient and public involvement

Individuals currently or formerly affected by either AUD or TUD were involved in the development of the study design including outcome measurements. Two research colleagues with insight from both perspectives were consulted and supported the development and implementation of the study. The chess-based cognitive remediation training was utilized in practice as described in the following including patients with diverse mental disorders. It therefore grew in correspondence with the patients' feedback. In addition, a pilot study with patient from an addiction rehabilitation center resulted in good to very good patient ratings regarding helpfulness and acceptance. We will disseminate study results to interested patients. Also all study participants will always be able to discuss open questions throughout

the process of the training with qualified research staff and they will receive feedback regarding the goals of the training and study and the background of the methods used for training and study examination.

No patients are involved in the recruitment procedure and conduct of the study and the burden of study participation was not assessed beforehand by patients.

Examination procedure

Eligible participants between 18 and 65 years will be informed about the purpose and all aspects of the study. They will be provided with written study information according to the ethics regulations. Participants will be able to ask questions regarding the study. Afterwards, written informed consent will be obtained. All participants can withdraw their consent at any time. Then, study exclusion- and inclusion criteria will be examined. To do so, a structured clinical interview (SCID-5-CV)[47] will be performed to assess a possible history of lifetime and current mental disorders. Individuals with a diagnosis of severe mental or personality disorders will be excluded, e.g., lifetime bipolar disorder or schizophrenia or current severe depression, post-traumatic stress disorder. Current mild or moderate mental or personality disorders, such as mild anxiety-, adaptation, personality disorders or depression, will be tolerated. Individuals with AUD are included in the study after controlled abstinence for at least 72 hours, including completion of medically supervised detoxification (treatment of withdrawal symptoms with short-acting benzodiazepines or chlormethiazole must have been completed for at least three days). Individuals with TUD will be included following the intention to quit smoking. A detailed list of all inclusion and exclusion criteria regarding AUD and TUD are shown in table 1. Following study inclusion, participants will be randomly assigned to either the control or experimental group.

At the baseline examination appointment (T1) all participants will provide sociodemographic information and perform several neuropsychological tasks. An fMRI assessment will then take place. Participants will also fill out several questionnaires directly after the baseline assessment. After the 6 week long intervention period - either standard treatment alone or with CB-CRT as therapy add-on - a second examination appointment (T2) takes place. All participants will perform the same neuropsychological tasks again and the same fMRI assessment as conducted in T1 will take place. Participants will also fill out the same questionnaires as for T1. During a follow-up period of 12 weeks following the intervention,

three telephone interviews (FU1, FU2, T3) will be conducted once a month. Instances of relapse and amount of tobacco or alcohol consumption will be documented. Beyond this, the same questionnaires as for T1 and T2 will be completed.

Please see figure 1 for a detailed description of the study procedure and tables 2 and 3 for list of assessments used, including fMRI and neuropsychological paradigms, and questionnaires.

Standard Treatment

All study participants (TUD and AUD) will follow their respective treatment as usual (TAU). With regards to TUD, a qualified smoking cessation group therapy with one therapy session per week (90 minutes) will be held by a trained and certified psychologist. This intervention is strongly recommended in the latest version of the S3 guidelines for tobacco use disorder[48]. A superior effect on smoking cessation was observed following group therapy compared to, e.g., self-help or less intense interventions[49]. During the qualified smoking cessation group therapy, interventions following a cognitive-behavioural psychotherapy approach will be applied[50]. Study participants with AUD will follow the respective in-house or day-clinic therapeutic programme, as recommended by the respective S3 guidelines for alcohol use disorder[51]. This standard treatment includes medical and psychological interventions.

Chess-based cognitive remediation training

The planned CB-CRT „Entrenamiento cognitivo a través del ajedrez (ECAM, „Cognitive training through chess“, https://ajedrezmagic.es/el-entrenamiento-cognitivo-a-traves-del-ajedrez/) consists of a battery of tasks and was developed by one of the co-authors (J. A. M.). The training battery, which is administered in a group setting using mainly a chess demonstration board, is designed to strengthen cognitive functioning in specific domains such as selective attention (figure 2a), short-term memory (figure 2b), focal attention, pattern recognition, visuospatial abilities, planification skills (figure 2c), and inhibition. Participants do not need to know the game of chess. They will receive general information about the rules and strategies used for the corresponding training day. Overall, metacognitive abilities are trained as well, e.g., by giving psychoeducational information regarding different concepts of cognitive functioning, questioning, and identifying the underlying cognitive process, and enhancing the awareness of before mentioned aspects. Participants perform most of the specific tasks in front of the group and, for a social reinforcement effect, everyone will applaud the respective

participant. Some of the tasks are conducted via paper-pencil. The training battery has been utilized for more than ten years by J.A.M and his colleagues as an add-on therapy for elderly individuals, children with autism and/or ADHD, individuals with Down Syndrome, mental and other disorders, and in adults with SUD. The scientific evaluation of the program is one of the goals of the current study.

In an unpublished pilot study in the rehabilitation clinic at Comunidad Terapéutica La Garrovilla, N = 26 patients with SUD (N = 22 male; substances: alcohol, opiates, cocaine, benzodiazepines, cannabis) were examined. CB-CRT was applied in a group setting twice a week for a duration of 90 minutes each. Cognitive functioning, especially in executive functions, was assessed at admission to the clinic at Comunidad Terapéutica La Garrovilla, Badajoz (Extremadura, Spain) and again after 14 weeks. The neuropsychological testing battery included measures of general processing speed (trail-making test A), cognitive flexibility (trail-making test B)[52], planning abilities (Tower of London)[53] and intelligence (Wechsler Adult Intelligence Scale, WAIS). Significant increases in performance were found after 14 weeks of treatment in general processing speed (trail-making test A; p = .001), cognitive flexibility (trail-making test B; p = .013), the Tower of London test (p = .001) as well as in the WAIS measures for verbal comprehension (“similarities”, p = .019) and for working memory (“letter-number sequencing”, p = .030, “digit span forward”, p = .044, “digit span backward”, p = .018, “digit span total”, p = .007). Performance in the WAIS measures “coding” (processing speed) and “matrix reasoning” (perceptual reasoning) did not differ significantly. In another sample of N = 15 patients receiving the chess-based add-on treatment for 3.5 months, subjective satisfaction was evaluated. On scales ranging from 1 (very unsatisfied / very poor) to 4 (very satisfied / very good), 73% of the patients rated the overall program as very good (i. e. score of 4). 67% of the patients found the program very helpful in treating their SUD (score of 4), 27% found it helpful (score of 3). Further, when asked how the program influenced other domains being negatively affected by SUD before admission, 53% found the program very supportive (score of 4), 27% found it supportive (score of 3). Besides this, 87% reported that the program helped them to increase their memory capabilities, 93% stated a subjective increase in attention performance, and 93% reported an enhancement in decision-making.

Self-rating Questionnaires

Self-rating questionnaires will be administered to address factors related to, e.g., impulsiveness and inhibitory control, mood, psychosocial functioning, as well as substance consumption, or craving. Please see Table 2 for a detailed list.

Neuropsychological assessments

Tasks investigating components of working memory (Wechsler Memory Scale-3)[54], decision-making (Iowa Gambling Task)[55], as well as mental flexibility (Dimensional Change Card Sort)[56] and attentional capacity (d2-R Test of Attention)[57] will be administered.

fMRI assessments

During the fMRI scanner examination, study participants will perform a stop-signal task[58], alcohol- and tobacco based cue-reactivity tasks[59, 60], an N-back task[61] and a resting-state MRI. Scanning will be performed with a 3T whole-body tomograph (MAGNETOM Prisma; Siemens, Erlangen, Germany). T2* weighted multi-band echo-planar images (mb-EPI) using a multi-band acceleration factor 6 will be acquired in a transversal orientation 20° clockwise to AC-PC-line covering the whole brain (TR = 869 ms, TE = 38 ms, 60 slices, slice thickness = 2.4 mm, voxel size 2.4 × 2.4 × 2.4 mm, no inter-slice gap, field of view (FoV) = 210 mm, matrix size 88 x 88, acquisition orientation T > C, interleaved slice order, acceleration factor slice = 6, flip angle = 58°, bandwidth = 1832 Hz/Px, prescan normalize, weak raw data filter, LeakBlock kernel, fat sat). This short TE and the 20° flip to AC-PC orientation is chosen to minimize susceptibility artefacts. Scanner sequences are provided by the Center for Magnetic Resonance Research (CMRR), University of Minnesota, Minneapolis, MN, USA (https://www.cmrr.umn.edu/multiband/)[62]. In addition, a T1-weighted 3D MPRAGE (Magnetization Prepared - RApid Gradient Echo) dataset consisting of 208 sagittal slices (slice thickness 1 mm, 1×1×1 mm voxel size, FOV 256 x 256 mm^2, TR= 2000ms, TE = 2.01 ms, TI = 800 ms, flip angle = 8°) will be acquired.

Endpoints

endpoints are changes in neural alcohol and tobacco cue-reactivity[59, 60] (e.g., reduction in substance-related activation of striatal brain regions), neural correlates of inhibition (stop-signal task)[63] (e.g., increased dorsolateral prefrontal neural activation) and working memory (N-back task)[61] (e.g., increased inferior frontal neural activation), as well as functional

connectivity within the salience network (SN; insula, anterior cingulate cortex) and executive control network (ECN; dorsolateral frontal and lateral posterior parietal cortices) using resting-state fMRI data. Also, working memory capacity (letter-number sequencing task of the Wechsler Memory Scale-3)[54], impulsivity (Barratt Impulsiveness Scale-15)[64, 65], mental flexibility (Dimensional Change Card Sort)[56], decision-making (Iowa Gambling Task)[55, 66] and attentional capacity (d2-R Test of Attention)[67], summarized as cognitive functioning, are endpoints of interest. Additionally, the duration until the first severe relapse (daily smoking of at least one cigarette at day, consumption of more than 48 grams (females) or 60 grams (males) of alcohol) during the follow-up periods and amount of substance consumption in case of a relapse as well as improvements in psychosocial functioning will be examined.

Sample size calculation

Using the software package G*Power[68] the sample size calculation was conducted for the main primary outcomes, i.e., neurobiological correlates underlying adaptations following the CB-CRT, where we expected a minimum effect size of f = 0.2 for all constructs (ANOVA with repeated measures, within- and between subject factors and interactions). In this case, ideal sample coverage would be 24 individuals per group (at 80% power, alpha-level 5%).

Data analysis plan

To analyse psychometric and neuropsychological data, SPSS (Statistics for Windows, Version 25.0. IBM Corp., Armonk, NY) will be used. The various dependent variables will be evaluated using multivariate analyses of variance with repeated measures. To counteract possible group differences at baseline, a percentage in change (divide by T1 values) or variable values at T1 can be incorporated in subsequent statistical analyses as a covariate. In addition, linear regression models will be calculated to examine the influence of confounding variables (for example, severity of tobacco or alcohol dependence) on the observed change in dependent variables as described previously (e.g., craving, task performance, psychosocial well-being). Cox-regression analyses, including, e.g., brain activation in the dorsolateral prefrontal or inferior frontal regions during inhibition and executive functioning, or the ventral striatum during cue reactivity tasks as predictors, will be conducted to examine the association with relapse. To analyse the fMRI data, SPM12 (Wellcome Department of Cognitive Neurology, London, UK) running under Matlab will be used. The pre-processing pipeline will include

motion correction, normalization to the Montreal Neurological Institute (MNI) template, and a spatial smoothing with Gaussian kernel of 8 mm full width at half maximum (FWHM) will be conducted. The pre-processed data will then be used for first- and second-level analyses. On the first level (within-subject), neural activation associated with task conditions (contrasts) will be modelled via a convolution with a canonical hemodynamic response function (HFR) following a general linear model (GLM). A high-pass filter to remove low-frequency components of fMRI time-series will be used. Depending on the fMRI tasks, specific contrasts regarding task conditions will be modelled as described in the above cited literature. On the second level (between-subject) and regarding the effects of group and time, paired t-tests (e.g., pre vs. post intervention within one group) and full factorial models will be used. Additionally, regression models including clinical variables, such as severity of TUD or AUD, will be calculated. To control for multiple statistical testing, we will use established correction procedures, e.g., whole brain family-wise error correction (FWE) for fMRI analyses or Bonferroni correction for other statistical analyses.

Hypotheses

Primary hypotheses

1. CB-CRT improves aberrant neural alcohol cue-reactivity (measured by alcohol and tobacco cue-reactivity fMRI tasks) in AUD/TUD in comparison to standard treatment alone
2. CB-CRT improves neuronal aberrations present when executing cognitive tasks (measured by N-back and stop-signal fMRI task) in individuals with AUD/TUD in comparison to standard treatment alone.
3. CB-CRT decreases functional connectivity within the salience network in individuals with AUD/TUD in comparison to standard treatment alone.
4. CB-CRT decreases functional connectivity within the executive control network in individuals with AUD/TUD in comparison to standard treatment alone.
5. CB-CRT improves cognitive functioning (measured by neuropsychological tasks) in AUD/TUD individuals in comparison to standard treatment alone.
6. CB-CRT improves psychosocial functioning (measured by, e.g., HSWBS, SWLS) in AUD/TUD individuals in comparison to standard treatment alone. CB-CRT influences

the treatment process, e.g., time to first severe relapse, for AUD/TUD individuals positively in comparison to standard treatment alone.

Secondary hypotheses

1. CB-CRT might be more efficacious in individuals with impaired cognitive functioning, low self-esteem, self-efficacy, and social support.
2. Chess as a three-week add-on therapy influences the treatment process, e.g., time to first severe relapse for AUD/TUD individuals moderated and mediated by cognitive, affective, and psychosocial factors.

Discussion

The here presented study aims to examine the effect of CB-CRT as treatment add-on on neurobiological processes but also neuropsychological and psychosocial functioning known to contribute to the development and maintenance of AUD and TUD. The effect of CB-CRT might also results in longer times of abstinence or reduced substance consumption. If CB-CRT as therapy add-on, as examined in this comprehensive study, shows to be more effective than standard treatment alone, this intervention might help to improve health behaviour in affected individuals.

Limitations with respect to the interpretability of the data might derive from the study design. We aim to examine the superior effect of CB-CRT compared to treatment as usual in therapy outcomes that might rely on neurobiological alterations following this training. As postulated by Sala and Gobet (69) a third, active control group might be needed to ultimately evaluate the chess-specific mechanisms and outcomes. Therefore and in case of successfully demonstrating a superior effect of our CB-CRT, a subsequent study might be needed to address this question. Further, even in light of our future results confirming a superior effect of CB-CRT as therapy add-on on neurobiological and neuropsychological processes, these improvements might to translate to longer abstinence or a reduction in the amount of substance consumption. Previously, this has been demonstrated in AUD: Even though an improvement in working memory functioning has been observed following an active working-memory training in patients with AUD, heavy drinking and neuropsychological functioning in other domains remained unchanged[39].

Since the described study includes a cognitive remediation training that exceeds merely training individual domains, we hope to counteract limitations of previous studies. Including

social (training in the group) and metacognitive aspects, the CB-CRT might generalize from altering neurobiological processing to behavioural changes, i.e. substance consumption.

Ethics and dissemination

The study was approved by the local Ethics Committee of the Medical Faculty Mannheim at the University of Heidelberg, Germany (reference number 2017-647N-MA). Before study inclusion and after a detailed explanation of all procedures, all participants will provide written informed consent. The study was registered in the Clinical Trials Register (trial identifier: NCT04057534) on December 8th, 2019. The study results will be disseminated by peer-review publications and conference presentations. Open-access publication is planned for all peer-reviewed publications. All participants are offered to receive a print of the final, published version of peer-reviewed publications. For protection of personal rights, and due to the sensitivity of the clinical and neuroimaging data, data will not be made publicly available. Upon direct request by other researchers and in mutual agreements (e.g., regarding data protection), anonymized data can be made available. Upon request, analysis procedures and codes will be shared with other researchers.

Risks associated with participation

Participants will be asked several questions regarding their substance consumption, mood, quality of life. They will additionally perform neuropsychological and fMRI tasks. Both excerpts a strain on the participants in terms of time and effort. Further, it may cause emotional discomfort in some participants. To counteract these possible negative consequences of study participations, the research team, also consisting of psychologists and psychotherapists in training, will regularly check if participants and evaluate their (dis)comfort. Contact to qualified clinicians will be made possible in case of severe emotional discomfort. Due to the length of the study appointments, we will offer participants the option to flexibly answer most of the questionnaires at home.

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Availability of data and materials

For protection of personal rights, and due to the sensitivity of the clinical and neuroimaging data, data will not be made publicly available. Upon direct request by other researchers and in mutual agreements (e.g., regarding data protection), anonymized data can be made available. Upon request, analysis procedures and codes will be shared with other researchers.

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Authors contributions

SVK designed the study. TW, GL, JH helped with designing the study. JAM developed the chess-based remediation training ECAM. GL, JH, RS, AJR, DK, AW, SVK, SG adapted the training. SG, GL, and SVK wrote the manuscript. All authors read and approved the manuscript.

Conflicts of interest

All authors have no conflict of interest to declare.

Tables

Table 1: Inclusion and exclusion criteria of the overall study sample. Specific criteria for AUD and TUD are highlighted.

Inclusion criteria		Exclusion criteria	
• Age between 18 and 65 years • Normal or corrected to normal vision • Signed written informed consent • Signed consent for data security		• Pregnancy • Positive alcohol test • Common exclusion criteria for MRI (e.g., metal, claustrophobia, epilepsy, adiposity) • Suicidality • Severe cognitive impairments (e.g., dementia) • Severe physical illness • Neurological disorders, history of brain injury • Therapy with methylphenidate within the last 8 weeks • Other mental disorders, except for mild or moderate anxiety-, adaptation-, post-traumatic stress-, personality-, attention deficit / hyperactivity disorders	
AUD	**TUD**	**AUD**	**TUD**
• AUD according to DSM-5 (more than 3 fulfilled criteria) • Currently in therapy for AUD (in-patient or outpatient therapy) • Abstinence from alcohol > 72h	• TUD according to DSM-5 (more than 3 fulfilled criteria) • Participation in smoking cessation therapy	• Other Axis I mental disorder except for mild, moderate or remitted depression, other substance use disorders if AUD is still the main diagnosis • Severe withdrawal symptoms (CIWA-Ar > 7; Sullivan et al. 1989) • Psychotropic medication within the last 14 days except for antidepressants or soporific and intake of medication for treating withdrawal effects until 3 days prior to study participation	• Other Axis I mental disorder except for mild or remitted depression, other mild substance use disorders (i.e., max. of 3 fulfilled DSM-5 criteria in the last 12 months) • Psychotropic medication within the last 14 days except for antidepressants

Note: AUD = Alcohol use disorder; TUD = Tobacco use disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders; MRI = Magnetic resonance imaging

Table 2: Self-rating questionnaires.

Questionnaire	Short term	Measurement Aim	Reference
Goal attainment scale	GAS	Abstinence-related goals	[70]
Rosenberg Scale		Self-esteem	[71]
General Self-Efficacy Scale	GSE	Self-efficacy	[72]
Perceived Social Support Questionnaire	F-SozU	Perceived social support	[73]
Habitual Subjective Well-Being Questionnaire	SWLS	Psychological well-being	[74]
Satisfaction with Life Scale	SWLS	Life satisfaction	[75]
Positive and Negative Affect Schedule	PANAS	Affect	[76]
State-Trait Anxiety Inventory		Anxiety	[77]
	STAI X2	Personality trait	
	STAI X1	Temporary state	
Beck Depression Inventory II	BDI II	Depression	[78, 79]
Percived Stress Scale	PSS	Perceived stress	[80]
Barratt Impulsiveness Scale	BIS-15	Impulsivity	[64, 65]
Adult ADHD Self-Report Scale-V1.1 Symptoms Checklist	ASRS-V1.1	ADHD symptoms	[81]
ADHD Self-Rating Scale	ADHD-SB	ADHD symptoms	[82]
Creature of Habit Scale	COHS	Automatic behaviour	[83]
Self-Report Habit Index	SRHI	Substance-related habits	[84]
Fagerström Test for Nicotine Dependence	FTND	Intensity of physical nicotine dependence	[85]
Alcohol Use Disorder Identification Test	AUDIT	Screening for alcohol use disorder	[86]
Clinical Institute Withdrawal Assessment for Alcohol	CIWA-Ar	Alcohol withdrawal symptoms	[87]
Form90		Alcohol or nicotine consumption	[88]
Visual Analog Craving Scales	VACS	Alcohol or nicotine craving	[89]
Obsessive Compulsive Drinking Scale	OCDS-G	Thoughts about alcohol and drinking behaviour	[90]
Alcohol Craving Questionnaire	ACQ-SF-R	Acute alcohol craving	[91]
Craving Automated Scale for Alcohol	CAS-A	Alcohol craving and automated drinking behaviour	[92]
Alcohol Urge Questionnaire	AUQ	Alcohol urges	[93]
Alcohol Dependence Scale	ADS	Severity of alcohol dependence	[94]
Questionnaire on Smoking Urges	QSU	Smoking urges	[95]
Craving Automated Scale for Cigarette Smoking	CAS-CS	Nicotine craving and automated smoking behaviour	[60]
Obsessive Compulsive Smoking Scale	OCSS	Thoughts about tobacco and smoking behaviour	[96]
Smoking Consequences Questionnaire for Adults	SCQ-A	Smoking outcome expectancies	[97]
Wisconsin Smoking Withdrawal Scale	WSWS	Nicotine withdrawal symptoms	[98]

Note: ADHD = Attention Deficit Hyperactivity Disorder.

Table 3: Schedule of measurement during study participation.

Measurement time point	**S**		**T1**		**T2**		**FU1**		**FU2**		**T3**	
Baseline	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
Demographic information	x	x	x	x								
Current medication*	x	x	x	x	x	x					x	x
Current somatic or mental conditions*	x	x	x	x	x	x					x	x
Structured Clinical Interview (SCID-5-CV)			x	x								
Smoking history			x	x								
Current smoking behavior*					x		x		x		x	x
Smoking Assessment Interview			x		x						x	
(Current) drinking behavior*		x		x		x		x		x	x	x
CIWA-Ar				x		x						
Current drug use*	x	x									x	x
Urine pregnancy and drugs screening			x	x	x	x						
Breath alcohol test			x	x	x	x						
Breath carbon monoxide test			x		x							
Goal attainment scaling			x	x	x	x						
Neuropsychology	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
MWT-B			x									
LNS-Task			x		x							
D2-R			x	x	x	x						
IGT			x	x	x	x						
DCCS			x	x	x	x						
Magnetic resonance imaging	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
Field-Map			x	x	x	x						
Resting-State			x	x	x	x						
NICUETINE			x	x	x	x						
N-Back			x	x	x	x						
SST			x	x	x	x						
ALCUE			x	x	x	x						
MPRAGE			x	x	x	x						
General questionnaires	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
PANAS			x	x	x	x	x	x	x	x	x	x
HSWBS			x	x	x	x						
GSE			x	x								
Rosenberg			x	x								
SWLS			x	x	x	x					x	x
FSozU			x	x								
Questionnaires - depression and anxiety	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
BDI II			x	x	x	x					x	x
PSS			x	x	x	x					x	x
STAI (X1)			x	x	x	x					x	x
STAI (X2)			x	x								
Questionnaires – impulsivity and ADHD	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
ASRS-v1.1			x	x	x	x						
ADHS-SB			x		x							
BIS-15			x	x	x	x					x	x
COHS			x	x								
Questionnaires - alcohol	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
ACQ-SF-R				x		x						x
ADS				x								
AUDIT	x	x										
AUQ				x		x		x		x		
CAS-A				x		x						x

OCDS-G				x		x		x		x		x		
SRHI (alcohol)				x		x						x		
VACS for MRI (alcohol)			x	x	x	x								
Questionnaires - tobacco	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**	**T**	**A**
OCSS			x		x		x		x		x			
CAS-CS			x	x	x						x			
QSU			x		x		x		x		x			
SCQ-A			x		x						x			
WSWS			x		x						x			
SRHI (tobacco)			x		x						x			
FTND			x	x	x						x			
VACS for MRI (tobacco)			x		x									

Note: S = Screening measurement, T1 = baseline and MRI assessment, T2 = MRI assessment, FU = monthly follow-ups via telephone; T3 = final follow-up via telephone; T = Tobacco use disorder; A = Alcohol use disorder; * self-report.

SCID = Structured Clinical Interview for DSM-5; AUDIT = Alcohol Use Disorder Identification Test; CIWA-AR = Clinical Institute Withdrawal Assessment; MWT-B = Multiple-choice vocabulary test (German version); LNS = Letter-Number-Sequencing (Wechsler-Memory Scale-3); D2-R = d2-R Test of Attention; IGT = Iowa Gambling Task; DCCS = Dimensional Change Card Sort; NICUETINE = fMRI tobacco cue-reactivity task; N-Back = N-back fMRI task; SST = Stop-Signal-Reaction-Time Task for fMRI; ALCUE = fMRI alcohol cue-reactivity task; MPRAGE = Magnetization Prepared - RApid Gradient Echo sequence; PANAS = Positive and Negative Affect Schedule; HSWBS = Habitual Subjective Well-Being Questionnaire; GSE = General Self-Efficacy Scale; Rosenberg = Rosenberg self-esteem scale; SWLS = Satisfaction with Life Scale; FSozU = Perceived Social Support Questionnaire; BDI-II = Beck-Depression Inventory; PSS = Perceived Stress Scale; STAI (X1,X2) = State / Trait Anxiety Inventory; ASRS-v1.1 = Adult ADHD Self-Report Scale Symptom Checklist, Part A; ADHS-SB = ADHD Self-rating Scale; BIS-15 = Barrett Impulsiveness Scale; COHS = Creature of Habit Scale; ACQ-SF-R = Alcohol Craving Questionnaire – short form revised; ADS = Alcohol Dependence Scale; AUQ = Alcohol Urge Questionnaire; CAS-A = Craving Automated Scale for Alcohol; OCDS-G = Obsessive Compulsive Drinking Scale - German; SRHI = Self-Report Habit Index (German translation, adapted for alcohol); VACS = Visual Analog Craving Scales for alcohol before and after fMRI for alcohol; OCSS = Obsessive Compulsive Smoking Scale; CAS-CS = Craving Automated Scale for Cigarette Smoking; QSU = Questionnaire on Smoking Urges; SCQ-A = Smoking Consequences Questionnaire for Adults; WSWS = Wisconsin Smoking Withdrawal Scale; SRHI = Self-Report Habit Index (tobacco); FTND = Fagerström Test for Nicotine Dependence; VACS = Visual Analog Craving Scales before and after fMRI for tobacco.

Figure captions

Figure 1: Study design. Following a screening, all participants will undergo a baseline (T1) appointment with diagnostic interviews, questionnaires, and functional magnetic resonance imaging measurements. Participants with tobacco or alcohol use disorder will be randomly assigned to the control group or intervention group. All participants will receive their respective treatment as usual. The intervention groups will additionally receive chess-based cognitive remediation training (CB-CRT). After the 6 week long treatment as usual with/ without CB-CRT (T2), the same measurements as for T1 will take place. During the follow-up period of 12 weeks, all participants will be contacted via telephone once a month.

Figure 2: Examples of the chess-based cognitive remediation training. 2a: Selective attention. Participants are asked to count the number of white knights on white squares (right answer: 5, squares: b1, b7, c6, d7, f1). During the training, participants receive 6 boards within a maximum of three minutes. **2b: Short term memory.** Participants are focused on the board and see the position for a few seconds up to one minute. Afterwards, the instructor asks the participants to reconstruct the position. Participants are asked to go to the front of the group and rebuild the position. 2**c: Executive functions, planification skills.** Participants must find out the shortest route the knight can go to capture the pawn. The knight must not stop on any square controlled by the rooks. The participant is asked to announce the number of moves before showing them on the board (correct answer: 4 moves – g5-e6-c7-b5-c3 or g5-e6-d4-b5-c3).

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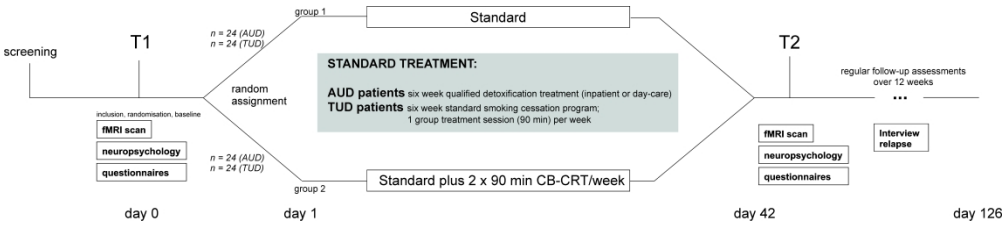

Figure 1: Study design.

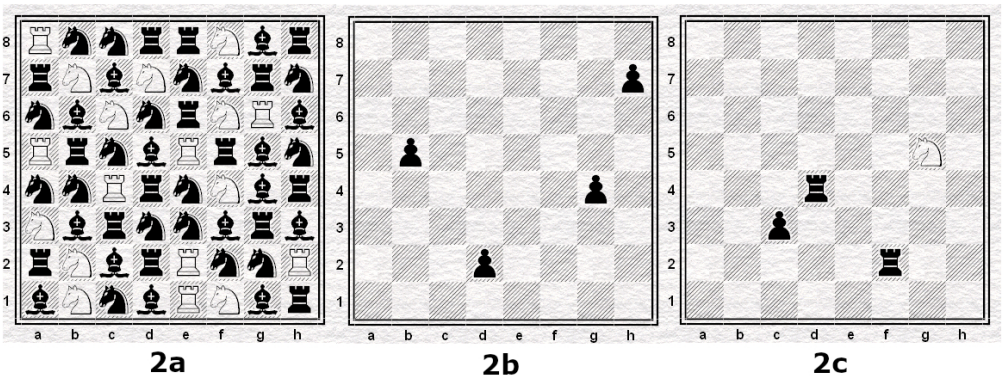

Figure 2: Examples of the chess-based cognitive remediation training.

98x38mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist accompanying the study protocol 'Effects of chess-based cognitive remediation training as therapy add-on in alcohol and tobacco use disorders: protocol of a randomized, controlled clinical fMRI trial'

Section/item	Page	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry
	n/a	All items from the World Health Organization Trial Registration Data Set
Protocol version	n/a	Date and version identifier
Funding	16	Sources and types of financial, material, and other support
Roles and responsibilities	1, 16	Names, affiliations, and roles of protocol contributors
	n/a	Name and contact information for the trial sponsor
	16	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	n/a	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	4-6	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6	Explanation for choice of comparators
Objectives	6,13-14	Specific objectives or hypotheses

Trial design	7-9	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	8, table 1	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	8-9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	n/a	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	n/a	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	n/a	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	11-12, table 2	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	8	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	12	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	7	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	n/a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	8	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	n/a	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	n/a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	n/a	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	11-12	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	n/a	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	n/a	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	12-13	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	n/a	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	12	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring		
Data monitoring	n/a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	n/a	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	n/a	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	n/a	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	2	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	2	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	6	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	n/a	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	8	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	16	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	16	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	n/a	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy	2	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	n/a	Authorship eligibility guidelines and any intended use of professional writers
	15	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	n/a	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	n/a	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable