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Effect of environmental enrichment on relapse rates in patients with severe alcohol use disorder: protocol for a randomised controlled trial

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ABSTRACT

Introduction Alcohol use disorder (AUD) ranks among the most prevalent psychiatric disorders worldwide. Despite current treatments, more than half of patients relapse within weeks after treatment. In animal models, exposure to environmental enrichment (EE) has been shown to be a promising approach to reduce relapse. However, controlled, multimodal EE is difficult to transpose to humans. To address this gap, this study aims at assessing the effectiveness of exposure to a newly designed EE protocol during AUD treatment in reducing relapse to alcohol use. Our EE will allow an enhancement of the standard intervention, and will combine several promising enrichment factors identified in the literature—physical activity, cognitive stimulation, mindfulness and virtual reality (VR).

Methods and analysis A randomised controlled trial involving 135 participants receiving treatment for severe AUD will be conducted. Patients will be randomised to an intervention enhancement group or a control group. The enhanced intervention will consist of six 40-min sessions of EE spread over 9 days. During the first 20 min of these sessions, patients will practise mindfulness in multisensory VR, in virtual environments designed to practise mindfulness and use it to regulate craving induced by virtual cues or stress. Then, participants will practise indoor cycling combined with cognitive training exercises. The control group will undergo standard management for AUD. The primary outcome is relapse assessed at 2 weeks after treatment, using a questionnaire and biological indicators. Relapse will be defined as drinking at least five drinks per occasion or drinking at least five times a week. It is predicted that the group receiving the EE intervention will have a lower relapse rate than the control group. The secondary outcomes are relapse at 1 month and 3 months after treatment, craving and drug-seeking behaviour, mindfulness skills acquisition and the effect of the intervention enhancement on the perceived richness of the daily environment, assessed by questionnaires and neuropsychological tasks.

Ethics and dissemination All participants have to give written informed consent to the investigator. This study is approved by the Ethics Committee Nord Ouest IV of Lille (reference number 2022-A01156-37). Results will be disseminated through presentations, peer-reviewed journals and seminar conferences. All information on ethical considerations and open science practices can be accessed at https://osf.io/b57uj/

Trial registration number NCT05577741.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first to attempt to transpose the complex environmental enrichment (EE) used in animal models to humans for the treatment of alcohol use disorder.
⇒ Our EE protocol is designed to target the main triggers of relapse, which are stress and cue reactivity.
⇒ Repeated assessments and follow-up during the period of vulnerability for alcohol-dependent patients allow a robust evaluation of the outcomes.
⇒ The EE used for this intervention does not include specific forms of social stimulation.
⇒ Neither the participants nor the therapist can be blinded to the treatment, as this trial includes complex behavioural interventions.

INTRODUCTION

Alcohol use disorder (AUD) is one of the most prevalent psychiatric disorders, affecting 107 million people worldwide.[1 2] It is associated with high morbidity and mortality, causing 3 million deaths per year.[2] Relapse is the most significant obstacle to rehabilitation. Despite the existence of several treatments, 85% of patients treated for AUD relapse, even after long periods of abstinence.[3] In particular, the first 3 months of abstinence constitute the period of greatest vulnerability,[4] and more than half of patients will consume their first drink (lapse) within 2 weeks.[5] Craving is one of the main predictors of relapse[6–9] and is triggered by drug use, drug-associated environmental cues and stress.[10–12] It is therefore necessary to manage craving, through therapy allowing patients to better handle daily stress and cue exposure.

Environmental enrichment

Environmental enrichment (EE) is a promising experimental paradigm to reduce craving and the risk of relapse. The role of the environment in the development and continuation of addictive behaviour is well demonstrated.[13–21] In addition, environmental conditions during periods of abstinence represent an interesting opportunity for intervention.[21] Preclinical studies have found that EE combining different types of stimulation can prevent the development and maintenance of addictive behaviours. EE combines complex social, cognitive and physical stimulation (a large cage, new toys, a racing wheel) that aim to improve sensory, cognitive and motor functions. In animal models of addiction (and for different types of drugs), housing addicted individuals in an EE during a period of abstinence led to extinction of the addictive behaviour and a reduced risk of relapse compared with control animals housed in standard cages.[18 22 23] This non-pharmacological strategy would prevent relapse by altering the stress response and drug-seeking behaviour, resulting in decreased brain reactivity to cues.[14 17–19] Behavioural and neurobiological evidence suggest that modulation of the reactivity to stress plays a major role in the effects of EE.[24 25]

Human studies have examined the effect of different aspects of EE, such as physical activity, cognitive or social stimulation, separately on addiction.[18] However, no study has integrated these different components into a model of EE to provide multimodal stimulation. Yet, preclinical studies suggest that cognitive and physical stimulation can induce additive or complementary action leading to greater neurogenesis when combined, which can produce better therapeutic results.[26]

Environmental components in the treatment of addiction

Different components of EE have already shown promising results in humans. Physical exercise has positive effects on methamphetamine,[27] alcohol[28] and nicotine addiction.[29–32] In particular, several studies have shown positive effects of exercise on stress, mood and craving in alcohol-dependent patients, suggesting that physical activity could be effective in treating addiction.[33] Regarding cognitive stimulation, studies that integrated cognitive training of several cognitive functions (attention, memory, executive functions) have revealed positive effects on different types of addiction, improving cognition, well-being and the compulsive aspect of craving.[34–37] Interestingly, there exist commercial solutions such as the cognitive bike (vélo-cognitif) that allow performing at the same time physical and cognitive exercise in comfortable, easy and safe conditions that are adapted to hospital settings.

A recent review highlights the potential of combining cognitive exercises with alternative interventions such as mindfulness that can impact both non-cognitive and cognitive processes, particularly executive functions known to be strongly impaired in alcohol-dependent patients.[26] Mindfulness practice allows training attentional reorientation, metacognition, inhibitory control, emotion regulation and interoception. Thus, mindfulness serves as cognitive–behavioural training that promotes well-being while targeting emotional regulation and addiction mechanisms.[38 39] Many studies have shown positive effects of mindfulness practice on stress levels.[40 41] In particular, the Mindfulness Based Stress Reduction programme is widely used to improve stress regulation by teaching people to practice mindfulness in stressful situations.[42] Furthermore, a number of studies suggest that mindfulness interventions allow the reduction of craving, drug consumption and the relapse rate in tobacco and alcohol addiction.[43 44] In addition, some authors have found that among the methods used in training executive functions, mindfulness and physical activity are particularly promising, facilitating a general improvement in tasks other than those used for training.[45] An intervention combining these different techniques could therefore be more effective in training the deregulated cognitive and affective processes involved in addiction.[26]

Virtual reality (VR) is increasingly used in medical protocols to enrich the environment of patients suffering from various cognitive disorders.[46 47] VR allows exposing patients to different levels of enrichment and stimulation in secure and controlled environments. Moreover, VR helps promote patients' well-being and stimulates them at the cognitive level.[48] Another benefit is that VR can simulate proximal and contextual cues of risky situations for patients (being in a bar or at a party with people drinking and offering alcohol).[49 50] Several studies have shown that exposure to cues in VR is particularly effective in inducing craving.[51–53] Therefore, VR is increasingly used for addiction treatment, mainly in cue exposure protocols, to try to extinguish the stimulus (cue) response (drug consumption) association.[54 55] In addition, an interesting feature of VR is that it can be used to induce stress,[56 57] a known trigger of craving and relapse.[12] VR could therefore allow patients to practise regulating their cravings induced by cues or stress in a secure setting, preparing them for a return to everyday life.

VR could facilitate mindfulness practice. Indeed, practicing mindfulness can be complicated for beginners, who may have difficulty staying focused.[58] In particular, many alcohol-dependent patients have comorbidities, such as depression[59 60]; these can lead to a loss of motivation that can make active participation on the part of the patient more difficult. One study showed that VR, as a very immersive technology, could compensate for these difficulties by facilitating the allocation of attentional resources to the virtual environment (VE), thus reducing distracting thoughts.[61] The combination of VR and mindfulness can therefore be an interesting tool to provide EE in humans. Practising mindfulness in VEs that induce craving through cues or stress could be particularly useful in training patients to learn how to cope with these situations in their real life.

Aims of the study

The main aim of this study is to assess the effectiveness of exposure to EE combining physical activity, cognitive activity using cognitive bikes and mindfulness in VR to prevent AUD relapse. Our randomised control trial will allocate half of the patients to a control group that will receive only the standard treatment for AUD and half to an intervention enhancement group that will receive several sessions of EE in addition to the standard treatment. We hypothesise that the relapse rate in the group receiving the EE intervention will be lower than in the control group at 2 weeks, 1 month and 3 months after the intervention or the 10th day of inclusion. We also expect the EE intervention to induce a greater decrease in patients' craving and drug-seeking behaviour than standard treatment. It is predicted that the EE intervention will improve patients' mindfulness skills. Finally, we believe that the intervention, by providing alternative rewarding stimuli to drug taking, should encourage a change in behaviour[24] and thus in lifestyle (modification of one's environment), and should therefore increase the perceived richness of the daily environment.

METHODS AND ANALYSIS

Trial design

This study is a randomised, controlled, non-blinded trial with two parallel arms comparing an EE intervention group to a control group following standard care. Participants will be randomised at a 1/1 ratio to one of two groups. Both groups will complete a battery of tests and questionnaires on the 1st day of their inclusion and on the 10th day to evaluate craving and mindfulness skills before and after the EE intervention. Follow-ups will be conducted at 2 weeks, 1 month and 3 months after treatment to assess relapse. In addition to these measurement sessions, the intervention enhancement group will carry out six EE sessions.

Study setting

This study will take place in the laboratories of the Pierre Deniker Intersectoral Clinical Research Unit in Psychiatry at the Henri Laborit University Hospital Centre (CHL) in Poitiers, France. The study will end as soon as the number n=135 participants is reached or at the end of the 2-year inclusion period.

Participants

One hundred and thirty-five patients undergoing alcohol treatment will be recruited from the Calliope Addiction Unit at the CHL, or from the University Hospital of Poitiers. The base rate of relapse at this site is estimated to be about 50% at 1 month and 60% at 3 months.[62] Calculation of the sample size is reported in the sample size section.

The inclusion criteria are as follows: patients aged 18–65 treated for alcohol addiction at the CHL in an open ward or at the University Hospital of Poitiers for at least 48 hours with severe AUD according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders classification; benefitting from social security personally or through a third party in accordance with French law on research involving humans; and having signed the informed consent form after having received written information.

The exclusion criteria are as follows: disabling cognitive impairment; susceptibility to cybersickness; cardiological pathologies that could compromise the participation of the patient (detected by an ECG); advanced pulmonary or renal diseases or any unstable and serious medical conditions that could compromise the participation of the patient (subject to the judgement of a doctor); hypertension; ataxia; uncompensated or unstable psychiatric pathology; pregnancy; breast feeding; simultaneous participation in another trial; any other current addiction except addiction to tobacco, Tetrahydrocannabinol and benzodiazepines; being an employee of the investigator or of the clinical study site; being a patient protected by law; not covered by state health insurance; and being unable to complete the questionnaire based on the opinion of the investigator.

Randomisation

Patients are randomised 1:1 to either the control or intervention EE enhancement group. A block randomisation is used with a block size of 4, using an allocation sequence generated from RStudio by a biostatistician.

Intervention

The enhanced intervention consists of six sessions of exposure to EE spread over 9 days (depending on the inclusion date). These sessions take place in addition to the standard intervention and are planned with the patient so as not to interfere with other activities (workshops or therapeutic meetings). The EE is produced using two innovative tools combining different types of stimulation:

The practice of mindfulness in multisensory VR

A total of six virtual environments (VEs) have been developed in collaboration with Sensiks (Amsterdam, Netherlands) using Unity software. An Oculus headset and two joysticks are used to interact with the VEs. To mimic real life and guarantee the participant's immersion, the following interactions are possible in the VEs using the joysticks: moving around the environment by teleportation, catching and throwing virtual objects and ordering a virtual drink using a menu. Teleportation consists of pointing the joystick at predetermined points in the environments, represented by white circles on the ground. When the user points to one of the circles, he/she is immediately teleported to that location, thus limiting the risk of cybersickness due to vection. For each VE, mindfulness instructions are broadcast to enable guided mindfulness while exploring the environments. The mindfulness instructions have been prerecorded by

Figure 1 Virtual environments presented: forest (VE 1), beach (VE 2), bar (VE 3), party (VE 4), parachute jump (VE 5), plane (VE 6).

a therapist specialising in therapeutic relaxation and can be found in online supplemental file 1. These instructions take into account the VE presented and guide the participant through the scenario.

Description of the VEs (figure 1):

Environments 1 and 2 represent relaxing natural places: a virtual forest for the former and a sandy beach for the latter. In these VEs, the participants can catch and throw natural objects (flowers, mushrooms, shells).

Environments 3 and 4 feature places with cues associated with alcohol consumption: bottles of alcohol and avatars drinking in an appropriate context. Mindfulness instructions guide the participant through the following scenario. For VE 3, after a walk down a virtual street, the participant has to buy a bottle of water in a store and then order a coffee in a bar. The participant can grab objects (bottle of alcohol, cigarettes, coins) and buy or order a drink using a virtual menu presenting several choices of alcohol or soft drinks. The scenario for VE 4 is a virtual party in a house. Some avatars dance, smoke and drink alcohol in the living room, and others sit and chat or play cards. The session consists of the participant sitting with them and then going to the kitchen to get a bottle of water. Interactions with objects are the same as in environment 3 (possibility to grab bottles of alcohol, cigarettes or decorative objects), and a menu allows selecting a drink from the fridge, including a glass of water, wine, beer or fruit juice.

Environments 5 and 6 present stressful contexts. The scenario for VE 5 consists of a virtual parachute jump. The participant is immersed in a virtual aeroplane environment with avatars showing signs of stress (frequently looking right, left or out the window; shaky hands; leaning forward), and they have to jump after them. The participant cannot move freely or grab objects in this environment. The scenario unfolds gradually for 20 min. After the jump, the participant falls into a void, their parachute opens and they gradually descend. At the end of the session, the participant is at ground level. For VE 6, the scene takes place in a virtual aeroplane environment in which there is turbulence. The participant can explore the plane by teleporting. An announcement warning of turbulence is broadcast, and the participant is teleported into a seat and can no longer move. The turbulence consists of shaking of the plane, and there is a thunderstorm, falling luggage and avatars expressing fear (looking right and left, holding their heads in their hands, screaming and sobbing). Once the turbulence has subsided, the participant can grab a book or a bottle of water using the joystick.

The VR sessions take place in a multisensory cabin that allows enriching the experience by potentiating the immersion and the experience of mindfulness. This cabin enables a more embodied and realistic experience by generating sounds, smells, air and heat (figure 2). This device (the Sensory reality pod) was designed by Sensiks as a modular framework that includes electronic modules and programmable actuators to generate the defined stimulations at the desired times. The modules and actuators are linked through a central device. The VR cabin measures 119×119×224 cm. This tool provides a multisensory experience that adapts to the VE presented. The appropriate smells (notably forest, beach, alcohol, tobacco, coffee, gasoline), sounds, airflow and heat are programmed for each VE and evolve according to the exploration of the environment or as the session progresses (eg, when moving in the sun in the VE, heaters are switched on).

For each of the six sessions, patients complete 20 min of guided mindfulness while exploring a VE. The first two sessions aim to teach participants the practice of mindfulness through immersion in relaxing environments (VEs 1 and 2). Next, to train the patients to better control craving induced by cues, they are gradually exposed to VEs containing cues meant to arouse the desire to consume alcohol (VEs 3 and 4). The aim is to get used to being confronted with cues without it precipitating consumption by learning to regulate cue-induced craving through mindfulness. Finally, to train the patients to regulate stress, a powerful inducer of craving and relapse,[12] they are gradually exposed to environments that can induce stress (VEs 5 and 6). Mindfulness instructions guide the patient to regulate stress and stress-induced craving. The goal of this stress induction is for patients to learn to better regulate their stress in daily life, thus reducing their risk of relapse. During VR mindfulness sessions, patients' cardiac and respiratory activity is monitored using a breathing belt and a heartbeat ear clip.

Performing cognitive exercises while cycling

The second tool used for this intervention is the cognitive bike (Vélo-cognitif, figure 3), designed by RevLim

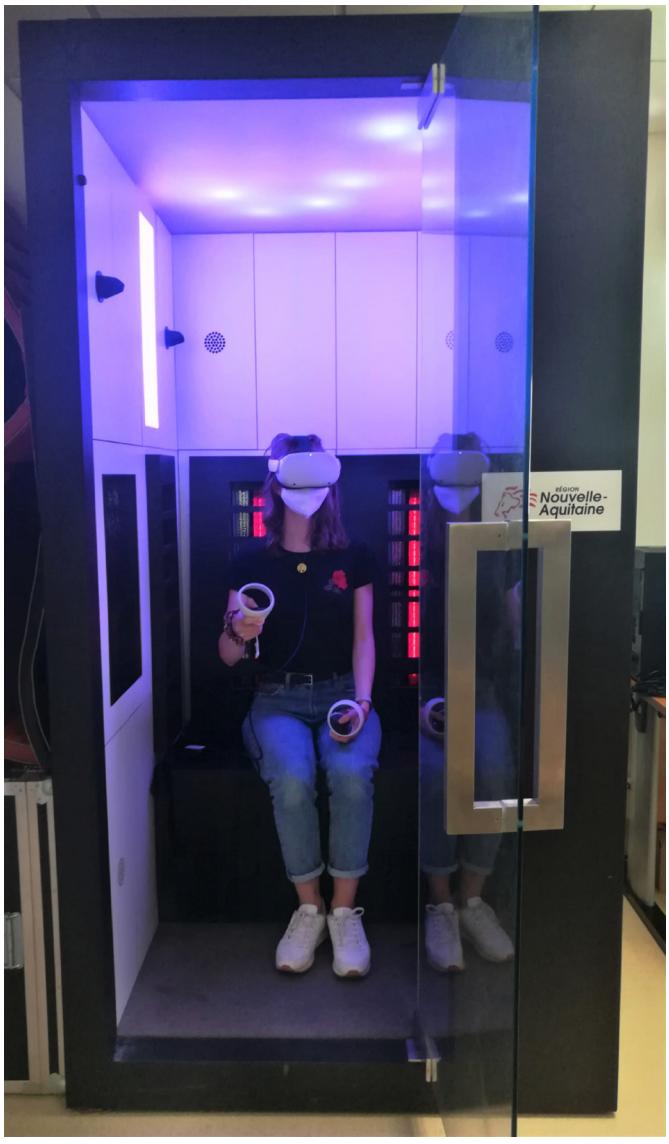

Figure 2 Sensory reality pod: Device created by Sensiks containing programmable actuators to generate different types of stimulation using heaters, an odour diffusion module connected to bottles containing fragrances, an audio system and fans. The authors (including the person pictured in the figure) declare that this photograph was illustrated by one of the coauthors, and grant permission and give their consent to BMJ open for the use of this photograph for publication, including print or web-based publications. The authors understand that with their authorisation the photograph can never be revoked.

to practise a cognitive and physical dual task. This tool combines an exercise bike and a touch pad offering cognitive training games. The bike has different levels of resistance. The cognitive exercises are designed by HappyNeuron, a network of scientific experts specialising in cognitive training. These exercises include training in inhibition, attention, memory and visuo-spatial skills through playful games of various difficulty levels. By simultaneously stimulating motor skills and cognition, this tool offers a playful activity in which the participants are able to see themself progressing and which could reduce

Figure 3 Vélo-cognitif (cognitive bike) consisting of an exercise bike to which a digital touch pad is attached to allow cognitive exercises to be performed while pedalling. The authors (including the person pictured in the figure) declare that this photograph was illustrated by one of the coauthors, and grant permission and give their consent to BMJ open for the use of this photograph for publication, including print or web-based publications. The authors understand that with their authorisation the photograph can never be revoked.

stress through physical activity.[63] In a pilot study using the cognitive bike with patients suffering from AUD, most patients reported having enjoyed the activity.[64] This tool could therefore help improve well-being and quality of life by providing a rewarding physical activity while exercising executive functions.

Control group

Patients in the control group are treated according to the standard protocol used at the Laborit Psychiatric Hospital. This consists of a clinical and biological examination performed by a health professional following the patient's admission to hospital. A treatment for withdrawal symptoms (benzodiazepines) is then administered under medical supervision. The patient benefits from individual medical and psychological monitoring. Workshops and therapeutic meetings are offered.

Measures

Primary outcome

The primary outcome is the proportion of individuals who relapsed 2 weeks after treatment. Relapse has been defined as drinking at least five drinks per occasion or drinking at least five times a week.[65 66] Maintenance of abstinence and relapse are usually assessed using

the Alcohol Timeline Followback (TLFB) assessment method.[67] However, this method relies on verbal reports and may thus be sensitive to under-reporting. Relapse is also assessed using biological indicators—a breathalyser, and a blood test for the measurements of carbohydrate deficient transferrin (CDT) and gamma-glutamyl transpeptidase (GGT). CDT is a glycoprotein synthesised by the liver and is a specific marker indicating the presence of alcohol in the blood. Elevated CDT levels suggest recent high alcohol consumption, particularly if other liver-associated enzymes (such as GGT) are elevated.[68] These measures will be used as combined indicators of relapse in order to corroborate the patient's report and to objectify the relapse, to avoid a possible reporting bias. Indeed, underestimation of consumption is frequent, and may be related to low insight or social desirability bias,[62 69 70] hence it is of interest to combine subjective with objective indicators of relapse. In this clinical trial, we will consider that a relapse occurred if at least one of the three indicators points to a relapse: (1) if in the TLFB the patient indicates consumption at least five times a week or at least five drinks per occasion; (2) if there is a significant increase in CDT and GGT since the day 10 blood test; or (3) if the breathalyser is positive. We will consider patients as non-relapsers if none of these indicators (TLFB, CDT and GGT, breathalyser) are positive.

Secondary outcomes

1. Mid-term relapse
   Relapse is assessed using the same measures at 1 month and 3 months.
2. Craving
   - Explicit craving, defined as the conscious desire to consume alcohol, is assessed in two ways:
     - Subjective craving during the past week is assessed using the Obsessive Compulsive Drinking Scale questionnaire,[71] which measures an individual's alcohol consumption and attempts to control it over the past week.
     - Craving induced by cues is assessed using the craving induction protocol of Fox *et al*.[72] This protocol induces craving through personalised cues, which consist of a short text written by the patient. This text should describe a memory of a situation of strong craving that led to consumption and should detail the context, the physical sensations and the state of mind during that scene. This half-page script is recorded by the experimenter, and then the audio is played to the patient during a second session. The patient indicates his level of craving before and after listening to the script on a Visual Analogue Scale ranging from 0 to 10, where 0 represents no desire to consume and 10 represents an extremely strong craving.
   - To obtain a behavioural assessment in relation to the automatic component of craving and drug-seeking behaviour, we also use three implicit measures (that will be combined into a single score of implicit craving):
     - Identification with the drug is assessed using a standard Implicit Association Test.[73] This test measures whether alcohol is more strongly associated with the self or others using images referring to alcohol or neutral images as target categories and words referring to the self or others as attribute categories (eg: 'me', 'I', 'myself', 'mine' or 'they', 'them', 'their', 'others').[73]
     - A test of the seeking for alcohol-related stimuli based on the probabilistic image choice task of Moeller *et al*[74] and adapted to alcohol is used. This test allows evaluating the preference for the drug among other reinforcers via four categories of images (drug, pleasant, unpleasant and neutral). There is a choice of four decks of cards, face down, each containing a majority of one of the image categories. A large image of the selected deck is presented on the screen for 2000 milliseconds, and then the subjects can select one of the decks again. A pseudo-randomisation described by Moeller *et al*[75] aims at reducing awareness of the identity of the deck while allowing a preference to be established. We adapted this task to alcohol addiction using images related to alcohol consumption (a glass of beer, a glass of wine, people drinking in a bar, etc).
     - Attentional bias towards alcohol is assessed using the task of Soleymani *et al*[76] a visual research test for alcohol-related stimuli (eye tracking). This task consists of freely viewing several sets of 16 images of alcoholic and non-alcoholic drinks, while an eye-tracker records the location of the first fixation and the total fixation time for each image. The strength of the attentional bias is determined by these two parameters.
3. Mindfulness
   - Mindfulness skills acquisition is measured using the Five Facets Mindfulness questionnaire.[77 78] This questionnaire assesses the tendency to be in a state of mindfulness in daily life based on five facets of mindfulness: observation (being attentive to one's internal/external states), description (being able to verbalise one's internal experiences), action with awareness (not automatic), non-judgment of internal and external experience (posture of acceptance, non-evaluative) and non-reactivity (detachment, non-response to internal states). We use the 15-item version of the questionnaire.[79 80]
   - The development of mindfulness skills is also assessed during mindfulness sessions using heart rate, respiratory rate and salivary cortisol measurements. These measures allow us to monitor the patient's attention to instructions, the stress induced by the en-

Table 1 Study schedule of enrolment and assessments by time points (Tn)

	Enrolment	Enhanced intervention		Post-intervention	Follow-ups		
Time point	T0	T1		T2	T3	T4	T5
Eligibility screening	X						
Informed consent	X						
Group allocation	X						
Primary outcome							
TLFB					X	X	X
Breathalyser					X	X	X
Blood test				X	X	X	X
Secondary outcomes							
OCDS	X				X	X	X
Craving induced by cues	X			X			
IAT	X			X			
Alcohol seeking	X			X			
Alcohol attentional bias	X			X			
MPSEQ	X				X	X	X
FFMQ	X		X	X			
Salivary cortisol	X		X				

FFMQ, Five Facets Mindfulness Questionnaire; IAT, Implicit Association Test; MPSEQ, Measurement of the Perception of a Stimulating Environment Questionnaire; OCDS, Obsessive Compulsive Drinking Scale; TLFB, Alcohol Timeline Followback .

vironments and whether mindfulness can effectively regulate this stress. These measurements also allow the calculation of heart rate variability associated with self-regulation skills, which is commonly used in research on mindfulness-based interventions.[81–83]

4. Richness of daily environment

We evaluate the effect of the intervention on the perceived richness of the daily environment. The perceived richness of the daily environment is assessed using the Measurement of the Perception of a Stimulating Environment Questionnaire (MPSEQ) (Chatard A, Barillot L, Besnier M, *et al*. Measurement of the Perception of a Stimulating Environment Questionnaire, unpublished, online supplemental file 2). Composed of 13 items, this questionnaire evaluates to what extent the individual perceives their environment as stimulating. Each item is a declarative statement referring to the stimulations, activities or satisfaction and entertainment that the person perceives or realises in their life (eg: 'My immediate environment is rich in sensations and stimulation of all kinds'). The individual expresses the extent to which they agree or disagree with each statement using a scale ranging from 1 to 7, with 1 corresponding to completely disagree and 7 to completely agree.

Study schedule

Summary table 1 (online supplemental file).

Potential participants are invited to a 15 min informative meeting. Eligibility screening is conducted, and patients are invited to participate after being provided a description of the study. A pretest in the VR cabin is offered to the patients to allow them to get acquainted with VR and to check that they do not shows signs of cybersickness.

Patients are reconvened (T0), and if they wish to participate in the study and if they meet all the eligibility criteria they sign the consent form and are randomly assigned to one of two groups. They complete baseline measures of their craving and salivary cortisol and complete questionnaires about their initial mindfulness skills and their perception of the richness of their daily environment (online supplemental table 1).

Intermediate measures take place for participants undergoing the intervention enhancement (T1). The acquisition of mindfulness skills is assessed after the second session of intervention enhancement. Salivary cortisol is measured after session 5 and session 6, which are expected to induce stress in the patient.

On the 10th day of inclusion or after completing the enhanced intervention (depending on the group) (T2), participants are seen again for a measurement session during which craving and mindfulness skills are assessed. A blood test is performed to obtain a baseline measurement of CDT and GGT. Relapse is assessed in both groups according to the method described in the measures section at 2 weeks (T3), 1 month (T4) and 3 months (T5) after T2.

Sample size

The required sample size was computed to have 80% statistical power to detect a significant reduction of relapse rate of at least 25% on our primary outcome (with

p<0.05, two-tailed). We considered a 25% reduction in relapse rate as the smallest effect size of interest in our study. This effect size seems realistic to us and appears to be the smallest effect size of clinical interest given the investment of material and human time in this intervention. The smallest effect size of interest is the smallest effect that (1) researchers personally care about, (2) is theoretically interesting or (3) has practical relevance.[84] The relapse rate on our site is about 50% on average after 1 month.[62] This is consistent with other studies in which nearly half of the patients relapsed in the weeks following hospital discharge for alcohol withdrawal.[85 86] With a relapse rate of 50% after 1 month, there is significant potential to reduce the relapse rate by 25%. It is quite possible that the intervention will have a much smaller effect size. However, if the relapse rate is not reduced by at least 25%, the intervention would be considered to have no efficacy or too low to be of clinical relevance.

The a priori power analysis for sample size indicates that the required sample size is 116 for our primary outcome. However, we will include 135 patients to compensate for possible missing data. For the secondary outcomes (craving, mindfulness skills, perceived richness of the daily environment) this sample size (N=135) provides adequate power (1-ß=0.82) to detect a medium effect size or a larger effect size (Cohen's d>0.50, with p<0.05 (two-sided).

Data analysis

Data analysts will be blind to the condition: the condition will be letter coded rather than explicitly 'control' or 'intervention'. All analyses will be conducted using both RStudio and SPSS V.23.0 software. A descriptive analysis of the study population will be performed. Qualitative variables will be expressed as a proportion with 95% CI. Quantitative variables will be expressed as mean and SD or as median and IQR. A value of p<0.05 (two-tailed) will be considered statistically significant. In intention-to-treat analyses, missing data will be simulated using a multiple-imputation technique with interim values.

The initial comparability resulting from the randomisation will be checked using tests appropriate to the distribution (parametric or non-parametric) and type (quantitative/qualitative) of the variables studied.

The primary outcome (relapse at 2 weeks) will be analysed using an independent sample proportion test (χ^2) comparing the differences according to the groups with a two-tailed alpha risk of 5%. The difference between the two groups for relapse at 1 month and 3 months (secondary outcomes) will be analysed in the same way. An independent sample t-test (Student's t-test) will be used on the other secondary outcomes (craving, mindfulness skills and perceived richness of the daily environment) to compare the differences before and after the enhanced intervention, and before and during the enhanced intervention for the intervention enhancement group (within-participant), with a two-tailed alpha risk of 5%.

ETHICS AND DISSEMINATION

All participants have to give written informed consent to the investigator. This study is approved by the Ethics Committee Nord Ouest IV of Lille (reference number 2022-A01156-37). Results will be disseminated through presentations, peer-reviewed journals and seminar conferences. All information on ethical considerations and open science practices can be accessed at https://osf.io/b57uj/.

PATIENT AND PUBLIC INVOLVEMENT

Patients or public were not involved in the design or conduct of the study.

DISCUSSION

This study aims at evaluating the effectiveness of exposure to EE sessions in reducing relapse in patients receiving treatment for AUD. This study is the first attempt to transpose the EE approach described in preclinical studies[24] combining different types of stimulation to humans. Our study should inform about the potential of this strategy to treat addiction by promoting long-term abstinence and reducing the incidence of relapse. Our EE provides rewarding stimulations as alternatives to drug taking while training the cognitive and emotional processes deregulated in AUD,[64] and provide skills that can be reused in daily life in stressful or cue-exposure situations to resist craving and avoid relapse.[18]

In terms of study limitations, it is possible that the acceptability of VR and mindfulness[87–90] can play a role in the effectiveness of the intervention enhancement. We have chosen to exclude people who show a cybersickness type of discomfort in the VR. Regarding mindfulness, repeated measures of mindfulness skills should help to control for this acceptability bias. Another limitation is that we chose to induce stress through VR during the last two EE sessions, even though stress is supposed to be a sort of functional opposite of EE and can therefore interfere with the enrichment procedure.[24 25] However, the sessions may be considered to be part of EE because they provide cognitive training to learn to regulate stress through mindfulness. Another possible weakness of the EE in this study is that it does not include additional social stimulation compared with standard treatment, while several animal studies have shown that social stimulation is an important component of EE,[24] and social support in humans is an important part of addiction treatment.[18] Therefore, further studies are needed to investigate whether a protocol of EE that includes more specific forms of social stimulation would be more effective than the present one. Finally, it will be important in the future to perform parametric studies to investigate whether more or fewer EE sessions can increase or decrease the benefits of this EE protocol.

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development of the protocol and study design. LVB wrote the first draft of this manuscript, which was revised and modified by all authors.

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