A personalized and smartphone-based, serious gaming application targeting cognitive impairments in alcohol use disorder: A piloting, double-blinded, randomized controlled trial

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Abstract

Background: Alcohol use disorder (AUD) is associated with cognitive impairments that are known to increase the risk of relapse and impede on the outcomes of conventional treatment. Digital cognitive training programs have been examined as a possible way of addressing these overlooked challenges. However, existing findings regarding the effectiveness of such training programs are divergent, and further studies are warranted to examine more engaging cognitive training programs using the latest technology. Furthermore, the clinical implementation of the training programs must be investigated to ensure the best and most effective treatment for patients with AUD. Using smartphone-based training built upon the principles of serious gaming would not only increase the accessibility of the program but it could also increase the motivation and compliance of the patients – potentially maximizing adherence to the training program.

Objective: The aim of the present pilot and feasibility study was to examine whether a smartphone application with gamified elements can improve cognitive and alcohol-related outcomes among patients with AUD when delivered as add-on to treatment-as-usual (TAU) and with minimal guidance from health-care practitioners. An adapted version of the Brain+ application was tested, and the feasibility and acceptability were assessed.

Methods: A total of 72 outpatients were randomized into either: Group A) experimental + TAU (n = 36), or Group B) sham + TAU (n = 36), and they had to complete a 1-month training program in addition to primary treatment. Cognitive functions and alcohol consumption were assessed at baseline, post-treatment, and at six months follow-up.

Results: The experimental group demonstrated significant improvements in processing speed and attention (P = .019) as well as working memory (P < .001). Although no significant differences were found between the two groups regarding clinical outcomes, a pattern favoring the experimental group was evident regarding the mean change reduction in alcohol consumption between the assessment at baseline and 6-months follow-up. The Brain+ application was feasible and accepted by both groups, and the experimental group adhered to the minimum training requirements.

Conclusions: The smartphone-based, serious gaming application showed promising effects for improving cognitive functions when delivered as add-on to TAU, but a larger scaled trial should be conducted in the future to assess its potential clinical effectiveness. Clinical Trial: A pre-registered and published research protocol is available (IRRID: RR2-10.3389/fpsyt.2021.727001)

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Trial Registration: IRRID: RR2-10.3389/fpsyt.2021.727001

Keywords: alcohol use disorder; cognitive impairment; cognitive training; serious gaming

Introduction

Individuals who have experienced long-term exposure to the neurotoxic effects of alcohol may show signs of cognitive impairment [1,2]. Patients with alcohol use disorder (AUD) experience partial recovery after successfully completing alcohol treatment and sustaining abstinence, but recent findings also suggest that some cognitive deficits persist in the domains for attention, working memory, and executive functions, and persevering impairments in learning and memory may even be measured after a year of abstinence [3-5]. It is well known that the active phases of AUD constituted by abuse/harmful use of alcohol or alcohol dependence and the initial phases of abstinence are characterized by impairments in cognitive functions [6]. Even after longer periods of abstinence,

patients with AUD still display a broad range of diffuse dysfunctions in controlled and effortful processes such as executive control, working memory, attention, and even episodic memory [1,3,7]. This evidence of a non-specific pattern of cognitive dysfunctions may be a result of the dissimilarities in characteristics across patients with AUD (e.g., comorbid mental disorders, premorbid cognitive functioning, severity of AUD, etc.) as well as the heterogenous methodology deployed by the different studies examining impairments in cognition [4].

Unimpaired effortful cognitive processes are important in the patients' everyday lives, but also in aiding them to exert control over their own impulses toward alcohol-related cues, thus increasing the likelihood of abstaining from alcohol [8]. Impairments in domains such as executive functions and working memory have been suggested to negatively impact treatment outcomes by lowering adherence to treatment as well as increasing the risk of relapse [9,10]. This highlights the importance of recovering a broad range of cognitive functions as these may be necessary for the successful treatment of AUD [11,12].

Therapeutic approaches focusing on restoring cognitive functions often consist of recurring, behavioral tasks that, if maintained for a longer period of time, result in neuroplastic changes, which in turn may be exhibited as improvements in daily activities [13]. Nevertheless, the effects of cognitive training can be assessed according to how closely the assessment resembles the training task. Increased performance in cognitive domains targeted by similar tasks to those pre-specified in the cognitive training program would be evident of a so called *near-transfer* effect [14]. On the other hand, improved performance in domains that are not related to the domains actively targeted by the training program are known as *far-transfer* effects [14].

The evidence of near-transfer effects among patients with AUD has been demonstrated using a wide range of different digital and computerized cognitive training programs [15-17]. These interventions have shown to be effective in improving different cognitive domains, but especially the domains for executive functions and working memory have been scrutinized [15,18,19]. Although evidence suggest that cognitive training designed to target specific domains such as working memory can provide near-transfer effects [19], an improvement in one domain may not optimally address the diffuse and heterogenous cognitive deficits that are evident in patients with AUD. In keeping with this notion, only preliminary findings are evident demonstrating far-transfer effects of cognitive training among patients with AUD [18]. This suggests that cognitive training programs focusing on a single domain, or a few closely related domains may be an inadequate strategy for targeting the wide range of cognitive impairments exhibited by patients with AUD. More complex programs consisting of a variety of training tasks each targeting a set of specific cognitive processes could thus be needed. These types of multi-domain, cognitive training programs have been shown to be feasible as well as capable of improving performance on a variety of cognitive tasks among patients with AUD [20-25]. Although the studies were mainly centered around the effects on higher-order cognitive functions such as working memory and problem solving, these findings suggest that using more multifaceted programs may be an effective method for improving a broader range of cognitive processes, which in turn could be beneficial for the abilities required for daily activities.

In the past decade, there has been a growing interest for uncovering *environmental-transfer* effects in studies examining cognitive training [16]. These types of effects can be deemed as a sub-category of far-transfer effects, but instead of only being related to cognitive domains, the effects can be generalized to improvements in clinical outcomes or in the patients' general functional abilities

(Harvey et al., 2018; Nixon & Lewis, 2019). For patients with AUD, evidence of environmental-transfer effects such as improvements in alcohol-related outcomes (e.g., reduced alcohol consumption or increased time of abstinence) is, however, still scarce [26]. A few studies focusing on domain-focused cognitive training [27-29] have examined the effects on alcohol consumption, but no significant reductions were found when compared to the control groups. Contrasting the findings for domain-focused programs, three studies utilized a training program targeting multiple domains [22,24,25], and two of these studies found that the intervention improved the rate of abstinence among the patients [22,25]. Although these findings were only reported in two of the studies, the effects suggest that interventions targeting a broader range of cognitive functions could be an important aspect for increasing environmental transfer.

Another possible factor that might explain the diverging findings regarding clinical outcomes could be the patients' level of motivation to change [30]. Motivation to complete a training program can be optimized if the tasks are kept adequately challenging while not being too overwhelming [31,32]. Earlier versions of computerized cognitive training have relied on less engaging paradigms based on an experimental setting [3,33]. Advancements in mobile health (mHealth) technology have made it easier to create a more personalized experience and more engaging training programs that incorporate gamification [34]and serious gaming elements [35,36]. Utilizing these technological aspects also allows the patients to access the training program from home, thus reducing the required visits at a treatment facility [33,35,37,38]. Nonetheless, the previous studies that examined environmental transfer of cognitive training did not fully incorporate the opportunities provided by mHealth technology.

The main aim of this pilot and feasibility study was to examine whether an unguided, smartphone-based, serious gaming application administered as add-on to conventional treatment can improve both cognitive and alcohol-related outcomes among patients with AUD. The secondary aim was to assess the acceptability and feasibility of the training program.

Methods

The present study was approved by the Research Ethics Committee for the Region of Southern Denmark (Project ID: S-20200199), and it was conducted in accordance with the Declaration of Helsinki [39]. This study was not registered in a public trials registry, but a protocol for the trial was published prior to the inclusion of patients [40]. No amendments were made to the original protocol, but minor changes to the total sample and age of the participants were incorporated into the study. Further, the reporting of this study is in accordance with the CONSORT 2010 Statement: updated guidelines for reporting parallel randomized trials [41].

Trial design

This pilot trial was conducted as a double-blinded, randomized controlled trial (RCT) with two parallel groups. An urn randomization technique was used without any stratification [42], and the allocation of patients to the groups was performed by an independent statistician. Although the present study was only a pilot trial without a formal power calculation, the goal was to include a minimum of 60 patients equally distributed across the two groups to approach a normal distribution in accordance with the central limit theorem. Based on prior trials that examined cognitive training [23,27,43], we expected an attrition rate of 20% (n =12 patients). Thus, 12 additional patients were recruited to ensure that we obtained the required sample size of 30 patients in each group.

Recruitment

Patients from the publicly financed, outpatient alcohol treatment clinic in Odense, Denmark were consecutively invited to take part in the study until a final sample of 72 patients was obtained. The recruitment took place between September 2021 and September 2022. All patients attending the clinic in Odense undergo a 3-month treatment program consisting of pharmacotherapy and/or psychotherapy, where the latter is based on manualized combined motivational interviewing and cognitive behavioral therapy [44]. During the primary treatment, a healthcare professional conducted a clinical assessment of the patients. This included an assessment of AUD and other substance use disorders (SUD) as well as severe mental (e.g., suicidal, manic, or psychotic symptoms), neurological (e.g., cognitive or motor symptoms that can challenge or impede performance in the cognitive training program), and somatic disorders according to the 10th version of the International Classification of Diseases (ICD-10) [45]. The Addiction Severity Index (ASI) was used to assess sociodemographic characteristics to generate an addiction severity profile for each patient. The profile covers seven modules including medical status, employment, drug use, alcohol use, legal status, family/social status, and psychiatric status [46].

Eligibility criteria

Patients were eligible to participate in the study if they: 1) had a confirmed diagnosis of AUD (i.e., harmful use/abuse or dependence); 2) had access to a smartphone or tablet that met the requirements for using the gamified cognitive training application; 3) were between 18 and 70 years of age; 4) spoke Danish; 5) provided informed consent to participate; and 6) had completed detoxification prior to study inclusion if deemed necessary. Patients were excluded if they had a diagnosis of SUD other than AUD, a severe mental disorder with suicidal, manic or psychotic symptoms, a neurological disorder (e.g., acquired brain injury, dementia, Parkinson's disease) including motoric impairments that can challenge or impede performance in the cognitive training program, or a terminal illness.

Procedure

After the initial clinical baseline interview and prior to initiating the primary treatment at the outpatient clinic (i.e., just after completing the detoxification program if deemed necessary), eligible patients were informed about the study by their health care providers. Patients who expressed interest in participating were referred to a research assistant who provided verbal and written information about the study following a standardized procedure. The research assistant scheduled a meeting with those patients who agreed to participate, which took place at the earliest the next day. At the meeting, the patients signed an informed consent form, and they were further screened for eligibility and allocated to an experimental or sham training group (see section on "Allocation and blinding"). Following this, a pre-treatment assessment of cognitive and clinical outcomes was conducted (see section on "Primary outcomes" and section on "Secondary outcomes"). Lastly, the research assistant assisted the patients with installing the application on their smartphone/tablet and provided instructions on how to use it (see section on "Instruction for the experimental and sham group").

Allocation and blinding

Eligible patients were consecutively randomized to one of two groups: A) an experimental version of the cognitive training program + treatment as usual (TAU) (n = 36), or B) a sham-version of the

cognitive training program + TAU (n = 36). The patients were blinded to their allocated group, and the research assistants who performed the randomization were also unaware of which version of the training application they helped to install on the patients' smartphone/tablet. This was achieved by assigning a random number to the two versions of the training application, and these two designated numbers were only known to an independent researcher who did not take part in the assessment of the patients.

Assessment and outcomes

Sociodemographic and clinical data were extracted from the outpatient clinic's clinical database containing data from the initial clinical assessments performed by the healthcare professionals. The research assessments were conducted by research assistants at study enrollment (T0), post-treatment (T1), and at 6-months follow-up (T2). The primary outcomes were assessed at T0 and T1 by means of the cognitive training application, the secondary outcomes were assessed at T0, T1 and T2, while the acceptability and feasibility of the application were only assessed once at T1.

Primary outcomes

Cognitive performance was measured with assessment versions of the various training games in Brain+ Alco-Recover. Since many of the games tapped into overlapping cognitive processes, the games were re-grouped across their pre-defined in-game categories. For the present study, the in-game category of *memory* was also split up so that working memory as well as learning and episodic memory could be assessed separately. The performance in four cognitive domains were pre-specified as executive functions (i.e., the in-game *Pathfinder*), processing speed and attention (i.e., the in-games *Perception Speed* and *Attention Island*), working memory (i.e., the in-games *Memory Lane* and *Bulky Codes*), and finally learning and episodic memory (i.e., the in-game *Remember Me*).

Bugs in the Brain+ application as well as difficulties with the implementation of a sham-version of the games for executive functions and episodic memory meant that the performance in these domains could not be assessed for the sham group. Thus, the executive and episodic memory domains were omitted, and the primary outcomes reported in this study was on two domains: processing speed/attention and working memory.

Secondary outcomes

Alcohol consumption was measured using the following two items derived from the alcohol module in the ASI: 1) days with any alcohol consumption in the past 30 days, and 2) days with excessive drinking (i.e., three units or more) in the past 30 days [46]. Mean craving level and highest craving level during the past week and the past 30 days was measured using the visual analogue scale (VAS) [47].

Intervention

The cognitive training application used in this study was adapted from the publicly available Brain+ Recover application [48], which was developed by neuropsychologists at the Centre for Traumatic Brain Injury, University of Copenhagen in collaboration with the company Brain+. Multiple versions of the Brain+ Recover application have been tested by other research groups [49-51]. For the present trial, the Brain+ Recover application was adapted, a sham-version was created, and the two adapted versions were renamed *Brain+ Alco-Recover*. The developer team at Brain+ ensured that the training

program in both the adapted versions consisted of the various types of games targeting multiple cognitive domains. To test the effects of the training program with high ecological validity, the Brain+ Alco-Recover application was used by the patients at home without any guidance from the researchers.

Experimental version of the cognitive training program

Six cognitive games were incorporated into the experimental version of the Brain+ Alco-Recover application. The games were grouped by the developers into four in-game categories (see section on "Primary outcomes"). The game *Attention Island* was categorized into *attention* (i.e., primarily targeting processing speed and visual attention), the game *Perception Speed* was categorized into *perception* (i.e., primarily targeting visual perception and visual attention), the game *Pathfinder* was categorized into *logic* (i.e., primarily targeting reasoning, problem solving, and planning skills), and finally, three games named *Bulky Codes*, *Memory Lane*, and *Remember Me* were categorized into *memory* (i.e., primarily targeting visual working memory, visual learning, and episodic memory).

The experimental version of Brain+ Alco-Recover consisted of a personalized training program initially created from the pre-assessment, and the difficulty level was adjusted to fit the patient's performance level measured during the pre-assessment. In this version, each time the patient successfully completed a game session, the results were visually presented, and the level of difficulty increased slightly to match the patient's current performance level. These incremental changes in difficulty included lower exposure time, additional items to recall, or more obstacles in the game, which would scale proportionally according to the patient's performance level. If the level of difficulty became too challenging and the patient could no longer complete the game session, the level of difficulty would decrease accordingly.

The personalized, daily training sessions consisted of the six different games, which were combined in two blocks of four games each. The training blocks alternated between the selection of games, but all the games appeared with the same frequency. The in-game algorithm ensured that the two blocks were personalized in terms of the duration of each game, and the cognitive domains in which the patient underperformed in during the pre-assessment were thus targeted for more intensive training. Each game took on average two minutes and 40 seconds to complete, but one training block lasted 10 minutes.

Instructions for the experimental and sham group

Based on other studies that examined a similar cognitive training program [21,23,27], patients in both the experimental and sham groups were instructed to use the application for 20 minutes a day, five days a week, for one month (i.e., a minimum of 400 minutes or six hours and 40 minutes of total in-game time for the entire intervention). Thus, the patients in both groups had to complete a training session consisting of two blocks lasting 10 minutes each (i.e., two blocks of four games each) to fulfil the minimum requirements for a daily training session. Adhering to this pre-defined training program would result in the completion of 20 training sessions (i.e., 40 training blocks) and this was equal to 150 games, which meant that each of the six different games appeared 25 times. These were the minimum requirements, and the patients were free to train more frequently if they wanted. During the study, a bug was discovered in the application that caused a game to skip (i.e., not marked as completed) if the patient closed the application in the middle of playing that game, and the next game

in the training block would then appear. This meant that the patients could play certain games more frequently than others resulting in an uneven distribution of completed games across the training blocks. To monitor the effects of this bug, the actual number of completed games was logged throughout the entire training period.

Since the present study used a basic version of the Brain+ Alco-Recover application to assess acceptability and feasibility, more advanced features such as notifications outside the application had not yet been developed. Due to the lack of a notification system and that the patients trained at home with no guidance, it was expected that the actual usage of the Brain+ Alco-Recover application and adherence to the training program would be much lower than the instructions provided to the patients.

Acceptability and feasibility of the cognitive training program

The acceptability of the Brain+ Alco-Recover application was determined by self-reported experience of the user interface as well as process outcomes. For the self-reported experience of the patients, the System Usability Scale (SUS) was used, which evaluates different elements of the user-interface and assesses the confidence of the user in using the training program [52].

The process outcomes were defined as the actual usage of the individual games in the training program For the experimental group, a minimum requirement of five completed game trials for each of the six games (i.e., four completed training sessions or 30 completed games in total) was deemed as acceptable and this was equal to approximately 80 minutes of total training time (i.e., 20% of the instructed duration for the pre-defined training program). At least half of the patients in the experimental group had to meet the minimum requirements for each game, which was set as the primary criterion for the process outcome. These requirements were not conveyed to the patients, and they were only informed about the instructed training program. The number of patients in the experimental group adhering to the instructed training program was also noted, but this was not used as a criterion for the acceptability outcome in the present study. It was not possible to calculate the actual duration for the usage of the Brain+ Alco-Recover application throughout the training period, thus only the logged number of completed games was used as the outcome. Although the error in the game *Pathfinder* and the lack of a sham version of the game *Remember Me* meant that these games could not be used as assessments for executive functions and episodic memory, respectively, the number of completed game trials for both games was still logged and used as an outcome for the acceptability of the entire training program.

To mitigate the bug that allowed the patients to skip certain games in a training block, a secondary criterion was set for the process outcome, and here it was required that two-thirds of all the patients had to complete at least 30 game trials regardless of the specific game type (i.e., meaning that the 30 completed games could consist of the same one or two games). Both these criteria for the acceptability outcomes were required for the experimental version of the Brain+ Alco-Recover application, but to detect possible differences between acceptability across the two versions of the training program, the number of patients adhering to these criteria was also noted for the sham version (i.e., except for the game *Remember Me*).

Statistical analyses

The baseline characteristics of patients in both study arms were summarized using means and standard deviations for continuous variables, and frequencies and percentages for categorical

variables. Differences between the two arms were assessed using independent samples *t*-tests for continuous variables, Chi-square tests for categorical variables, and the Mann-Whitney U test for non-normally distributed continuous variables.

The primary outcomes of the three cognitive domains as well as the *brain score* for the individual cognitive games were evaluated with independent samples *t*-tests by analyzing the differences in mean change between the baseline assessment and the assessment during the patients' last training session. The secondary clinical outcomes were evaluated with linear mixed models. These models incorporated data collected at baseline, post-treatment, and at 6-months follow-up for the secondary outcome measures, which included number of drinking days (DD), number of heavy drinking days (HDD), mean craving level (MCL), and highest craving level (HCL). The linear mixed models used the patient number as a random effect to account for within-subject correlation and time (i.e., DD, HDD, MCL, HCL at T0, T1, and at T2; cognitive assessment at T0 and T1). The model also included a time by randomization arm interaction as fixed effects to evaluate differential changes over time between the experimental and the sham group. Model assumptions were checked to ensure appropriate fit and interpretation of the results. In some cases, robust variance-covariance estimation was used to adjust for slight misspecifications. The analyses of primary outcomes were conducted as both intention-to-treat and as per-protocol (i.e., the minimum acceptable number of five completed game trials for each game), and the secondary outcomes as well as the feasibility and acceptability outcome were conducted as intention-to-treat only. The statistical analyses were performed using Stata version 18. A significance level of $P < .05$ was considered statistically significant for all tests.

Results

A total of 72 patients were randomized to either the experimental group ($n = 36$) or the sham group ($n = 36$). One patient in the experimental group withdrew consent to participate after the baseline assessment and thus data for this person were deleted (see Figure 1). Fifty patients completed the post-treatment assessment (i.e., experimental group: $n = 29$; sham group: $n = 21$), and 43 patients completed the 6-months follow-up assessment (i.e., experimental group: $n = 25$; sham group: $n = 18$).

[FIGURE 1]

Patient characteristics

No significant differences were found between the experimental and sham groups regarding age, gender, education, employment, and clinical variables (see Table 1). More than half of the patients were male (74.6%; $n = 53$), and the overall mean age of the patients was 43.3 years ($SD = 10.9$). Three of the included patients were 64, 67, and 70 years old, hence deviating from the eligibility criteria specified in the pre-registered protocol. Concerning the clinical variables, over 90% of the patients in both groups had an AUD (i.e., F10.2 diagnosis of alcohol dependence in the ICD-10), while the remaining patients fulfilled the criteria for harmful use of alcohol (i.e., F10.1 diagnosis in the ICD-10). Approximately 60% of the patients in both groups reported having previously received outpatient treatment for alcohol misuse. Previous inpatient treatment for alcohol misuse was reported less frequently, with only 9% of the patients in the experimental group and 8% in the sham group reporting this. The age of onset of heavy drinking was approximately 28 years in both groups.

Cognitive domain scores at baseline

The cognitive assessment revealed significant differences between the experimental and sham groups at baseline (see Table 1) in the domain for processing speed and attention as well as the domain for working memory (*p*s < .001). The experimental group performed better in the domain for processing speed and attention (*M* = 440.6, *SD* = 166.3; *n* = 17) compared to the sham group (*M* = 70.4, *SD* = 70.5; *n* = 22). Further, the average scores on the two individual games were significantly higher in the experimental group (*Attention Island*: *M* = 86.3, *SD* = 71.8; *n* = 13 and *Speed Perception*: *M* = 650.1, *SD* = 152.1; *n* = 17) compared to the sham group (*Attention Island*: *M* = 12.3, *SD* = 4.3; *n* = 22 and *Speed Perception*: *M* = 208.6, *SD* = 134.5; *n* = 13). The experimental group performed better in the domain for working memory (*M* = 210.3, *SD* = 36.8; *n* = 23) compared to the sham group (*M* = 127.4, *SD* = 7.7; *n* = 23). Moreover, the average scores on the two individual games were significantly higher in the experimental group (*Bulky Codes*: *M* = 212.3, *SD* = 39.8; *n* = 18 and *Memory Lane*: *M* = 204.8, SD = 44.8; *n* = 23) compared to the sham group (*Bulky Codes*: *M* = 137.2, *SD* = 10.7; *n* = 17; *Memory Lane*: *M* = 121.9, *SD* = 6.1; *n* = 22).

Table 1. Baseline Characteristics of the Patients

	Experimental	Sham	
	n = 35	*n = 36*	*P* value
Sociodemographic variables			
Age, mean (*SD*)	45.3 (10.1)	41.4 (11.5)	.14
Gender			.78
Male	27 (77%)	26 (72%)	
Female	8 (23%)	9 (25%)	
Clinical variables			
Diagnosis			
Harmful use (F10.1)	2 (6%)	2 (6%)	
Alcohol dependence (F10.2)	33 (94%)	33 (92%)	
Previous treatment for AM			
Yes	23 (66%)	22 (61%)	
No	12 (34%)	13 (36%)	
Age of onset of HD, mean (*SD*)	28.3 (10.8)	28.1 (11.0)	.92
DD in the past 30 days, mean (*SD*)	17.9 (10.8)	14.8 (10.6)	.23
HDD in the past 30 days, mean (*SD*)	16.5 (10.6)	13.7 (11.1)	.29
ACL in the past 30 days, mean (*SD*)	3.9 (2.6)	4.1 (2.7)	.72
HCL in the past 30 days, mean (*SD*)	5.4 (3.4)	5.3 (3.4)	.93
Cognitive variables			
PSA domain, mean (*SD*)	440.6 (166.3)	70.4 (70.5)	< .001
Attention Island, mean (*SD*)	86.3 (71.8)	12.3 (4.3)	< .001
Speed Perception, mean (*SD*)	650.1 (152.1)	208.6 (134.5)	< .001
WM domain, mean (*SD*)	210.3 (36.8)	127.4 (7.7)	< .001
Bulky Codes, mean (*SD*)	212.3 (39.8)	137.2 (10.7)	< .001
Memory Lane, mean (*SD*)	204.8 (44.8)	121.9 (6.1)	< .001

Note. ACL, average craving level; AM, alcohol misuse; DD, drinking days; HCL, highest craving level; HD, heavy drinking; HDD, heavy drinking days; PSA, processing speed and attention; SD, standard deviation; WM, working memory

Alcohol consumption and craving at baseline

The experimental group reported an average of 28.3 DD and 17.9 HDD in the past 30 days. The corresponding numbers in the sham group were slightly lower (DD: 14.8; HDD: 13.7). Regarding craving level measured using a 10-point VAS scale (0 = no craving; 10 = severe craving), the average craving level in the past 30 days was approximately 4 in both groups, while the highest craving level in the past 30 days was approximately 5 in both groups.

Outcomes for cognitive functions

Comparisons between the baseline and post-treatment assessments (see figure 2) showed significant differences between the two groups in the domain for processing speed and attention (P = .019) as well as the domain for working memory (P < .001). Closer inspection revealed that the differences were driven by higher mean change scores in the experimental group (processing speed and attention: M = 9.93, 95% CI [-61.2; 81.0] and working memory: M = 134.8, 95% CI [102.2; 167.5]) compared to the sham group (processing speed and attention: M = -72.8, 95% CI[-100.1; -45.6]; and working memory (M = 38.6, 95% CI [22.8; 54.4]). Regarding the individual games in these domains, significant differences were only present for *Bulky Codes* (P < .001) and *Memory Lane* (P < .001), which were driven by improvements in the experimental group (i.e., *Bulky Codes: M* = 131.4, 95% CI [95.2; 167.6] and *Memory Lane: M* = 155.8, 95% CI [123.5; 188.2]) compared to the sham group (i.e., *Bulky Codes: M* = 38.1, 95% CI [27.7; 48.5] and *Memory Lane: M* = 50.4, 95% CI [32.9; 67.8]).

In the PP-analyses, significant differences were found for the same domains as in the ITT-analyses, and these included processing speed and attention (P < .001) and working memory (P < .001). These differences were driven by higher mean change scores in the experimental group (processing speed and attention: M = 38.7, 95% CI [-35.9; 113.4] and working memory: M = 156.56, 95% CI [119.8; 193.32]) relative to the sham group (processing speed and attention: M = -106.2, 95% CI [-143.3; -69.0] and working memory: M = 55.7, 95% CI [45.6; 65.8]).

[FIGURE 2]

Examining the improvements in cognitive performance on the individual games, significant mean changes favoring the experimental group were present for *Attention Island (M* = 31.77, 95% CI [24.8; 38.7], P < .001), *Bulky Codes* (M = 115.5, 95% CI [76.9; 154.2], P < .001), and *Memory Lane (M* = 88.5, 95% CI [43.1; 133.8]), whereas no significant improvements were found for *Speed Perception* (M = 95.4, 95% CI [-45.7; 236.5], P = .185).

Outcomes for alcohol consumption and craving

No significant differences between baseline, post-treatment, and 6-months follow-up assessments were observed between the two groups regarding DD, HDD, average craving level, and highest craving level (see Figure 3). The mean difference from baseline to post-treatment assessment in alcohol consumption (DD: M = 0.87, 95% CI [-1.54; 3.27], P = 0.48; HDD: M = 0.85, 95% CI [-1.30; 3.01], P = .44) in favor of the sham group (M = -14.13, 95% CI [-16.67; -11.59]) rather than the experimental group (M = -13.27, 95% CI [-16.53; -10.00]). This was also evident for the mean craving level (MCL: 0.85, 95% CI [-0.69; 2.39], P = .28) which also showed a larger reduction in the sham group (M = -13.74, 95% CI [-16.32; -11.15]) rather than the experimental group (M = -12.88, 95% CI [-15.98; -9.78]).

[FIGURE 3]

The comparison between the baseline and the 6-months follow-up assessment revealed a similar pattern, with no significant differences between the two groups regarding DD (*M* = -0.96, 95% CI [-6.62; 4.70], *P* = .74), HDD (*M* = -0.99, 95% CI [-5.32; 3.33], *P* = .65), average craving level (*M* = 0.49, 95% CI [-1.47; 2.45], *P* = .62), and highest craving level (*M* = 0.66, 95% CI [-1.48; 2.79], *P* = .55). The mean difference at 6-months follow-up indicated a pattern that favored the experimental group for alcohol consumption (DD: *M* = -11.44, 95% CI [-15.00; -7.88]; HDD: *M* = -12.37, 95% CI [-15.54; -9.19]) relative to the sham group (DD: *M* = -10.48, 95% CI [-16.10; -4.86]; HDD: *M* = -11.38, 95% CI [-16.13; -6.62]), but there was no indication of a direction favoring one of the two groups for craving.

Brain+ Alco-Recover usability and number of completed games

Only 23.6% of the patients completed the SUS, but the overall experience with the Brain+ Alco-Recover application was well-received by these patients in both groups, and no significant difference was found between the ratings of the two different versions of the application (*P* = .17). This was indicated by a good usability rating with a mean total score of 74.6 (SD = 17.6) in the experimental group, while the sham group rated the usability of the training program as excellent with a mean total score of 81.5 (*SD* = 11.9).

The first criterion specifying that more than half of the patients had to fulfil the minimum requirement of five completed game trials for each of the games was reached in five out of the six games in the experimental version of the Brain+ Alco-Recover application (see supplementary material, Table S1). The game that did not meet this criterion was *Attention Island*, where only 37.1% of the patients (*n* = 13) completed the five required game trials. In the sham version of the application, the criterion was reached in four out of the five games. The game that did not meet the criterion was *Bulky Codes*, where 48% of the patients completed the five required game trials. There was no significant difference between the two groups regarding the number of completed game trials, the only exception being that significantly more patients in the sham group completed the minimum number of required game trials for *Attention Island* (*n* = 13, 65.7%) compared to the experimental group (*P* = .043). The second criterion specifying that more than two-thirds of the patients had to complete a minimum of 30 game trials regardless of game type was reached in both groups. In the experimental group, 74.3 % of the patients (*n* = 26) completed a minimum of 30 game trials, and the corresponding percentage in the sham group was 66.7 % (*n* = 24). The average number of game trials completed by the patients fulfilling this criterion was 217.4 trials in the experimental group (i.e., approximately a total of 577 minutes of training time) and 345.6 trials in the sham group (i.e., approximately a total of 919 minutes of training time).

Finally, the primary analyses for the acceptability outcome were followed up with secondary analyses to explore the number of patients who completed the required training duration or the 150 games regardless of game type. The analyses showed that 31.4 % (*n* =11) and 33.4% (*n* =12) of the patients in the experimental group and sham group, respectively, reached this requirement (see supplementary material, Table S2, more information on the individual games).

Discussion

The present pilot and feasibility study provides the most recent evidence on the potential usability and effectiveness of an unguided, smartphone-based, serious gaming application administered as add-on to conventional treatment among patients with AUD. The Brain+ Alco-Recover application was deemed feasible and accepted by the patients. Further, the experimental group exhibited significant improvements in attention and working memory compared to the sham group. Despite these promising effects, no significant differences were found between the two groups regarding clinical outcomes. Nonetheless, the observed reduction in alcohol consumption in the experimental group suggests that this type of cognitive training could potentially improve long-term clinical outcomes.

The near-transfer improvements in processing speed, attention, and working memory exhibited by the experimental group in the present study corroborates findings from previous trials that demonstrated near-transfer effects using similar multifaceted cognitive training programs for AUD [22,25]. Nonetheless, due to the technical issues that arose when developing a sham version targeting executive functions and episodic memory, our findings cannot be fully extended to a broader range of cognitive domains. In extension of the previous point, this also means that the training program in the present study was skewed towards targeting specific cognitive functions such as working memory. In keeping with this notion, other studies that examined cognitive training focusing specifically on attention and working memory were able to demonstrate far-transfer improvements in episodic memory e.g., [43,53]. It has also been suggested that cognitive functions do not work independently of each other, and tasks designed to train verbal memory are still highly dependent on the ability to direct one's attention and working memory resources to process and store information [16]. Thus, it could be hypothesized that even though the patients in the present study did not specifically train episodic memory, improvements in attention and working memory could manifest as improvements in other domains as well. However, the use of a cognitive assessment relying solely on the in-game, pre-assessment function impedes the assessment of whether these near-transfer effects can be conveyed into distal domains not actively trained in the current version of the Brain+ Alco-Recover application. Other studies have demonstrated cognitive improvements [21,23] by the means of the *Mini-Mental State Examination* (MMSE) [54], which suggests that this instrument could be used to assess far-transfer effects of cognitive training. Additionally, standardized screening tools may even be more pertinent to use among subgroups of patients suffering from severe AUD and widespread cognitive deficits, since these patients have been shown to be highly receptive to the remediating effects of cognitive training [13,14,16].

Our findings showed that the cognitive training program did not result in statistically significant improvements in clinical outcomes, however, small and clinically relevant changes in alcohol consumption were observed. By inspecting the reduction in the mean number of DD and HDD, the experimental group did exhibit close to a 10% reduction in alcohol consumption. Although a previous study by Kumar and colleges [25] with a comparable sample size (n = 50) was able to detect improved abstinence rates, we cannot rule out a potential type-II error concerning our present findings, meaning that the detection of significant differences might have required a larger trial. Additionally, the cognitive training program in the study by Kumar and colleges [25] was delivered in groups combined with yoga, breathing exercises, and psychoeducation, which resulted in a more guided and structured intervention that could potentially have induced a synergistic effect of the

different treatment elements. In contrast, other research groups have failed to demonstrate significant improvements in clinical outcomes [27-29,55], which corroborates the findings of the present study. Still, most of these studies included small sample sizes ($n \leq 60$), and one research group [27] did identify a trend for reduction in units per drinking day ($P = .070$), which could have been due to a lack of power. The training program used in the study by Khemiri, and colleges [27] focused more on training tasks selectively targeting working memory, but as in the present study, the patients used the training program at home with minimal guidance from the researchers. When aggregating these similarities, it could indicate that cognitive training programs, even when administered outside a treatment facility, may have clinically relevant effects among patients with AUD. However, the lack of evidence for environmental transfer of the training program in the present study could also support the notion that cognitive training programs are too reductionistic to comprise the complexity needed for behavioral changes to be transferred to real-world scenarios [14-16].

To date, studies that examined the effects of cognitive training with gamified elements [20,21,27,28,43,56,57] and studies that administered the cognitive training using mHealth technology [20,21] have shown that these means are generally feasible and accepted by the patients. In line with these previous findings, this study showed that the Brain+ Alco-Recover application was easy to use and accepted by the patients, which points to the training program being a feasible add-on to the existing conventional treatment for AUD. This provides further support for the use of smartphone-based technology, whereby the implementation of gamified elements can increase the motivation and engagement among patients with various mental disorders and potentially increase the overall adherence to the treatment [35,37,58].

Despite the promising results regarding the acceptability of the cognitive training program in this study, these were based on a minimum training requirement due to the unguided and home-based treatment delivery, and only one third of the patients adhered to the pre-instructed training program. This could be indicative of fundamental issues with the game design of the training program and the means of administration. Both aspects can be directly implicated in the motivation and engagement of the patients. It has been proposed that a constant display of frustrating training elements or display of negative scores may induce a state of failure and disbelief and thereby reduce the patients' self-efficacy [30]. This poses a potential threat to the effectiveness of the design of smartphone-based cognitive training programs, as one needs to balance the incentive to push the performance of the patients by constantly increasing the level of difficulty while ensuring that the patients receive an adequate amount of positive reinforcement. Even if the design of the game is not fully personalized and the training is perceived as being too difficult for the patient, this could be compensated for by implementing the training into existing treatment programs in which a health professional could encourage and coach the patient during the training program. In fact, previous studies have shown that administering the cognitive training program in an environment in which the patient receives support to maintain his or her treatment goals can cultivate the effects of cognitive training [1,21,23,43].

Although the cognitive training program was administered as add-on to conventional treatment, the patients in this present study were outpatients, and they used the application on their personal devices at home without the assistance or guidance from a health professional. This was implemented to optimize the ecological validity of the training program, but this could have had adverse effects on the proportion of patients adhering to the pre-instructed training program since it may have been too difficult for the patients to structure and incorporate the training sessions into

their everyday lives. Still, there are findings that suggest that outpatients with AUD can adhere to an unguided training program administered at home [21,27]. This highlights the importance of balancing the optimal training conditions between a highly structured clinical setting and a more unguided approach, where the patient can perform the training sessions under well-known and relaxed conditions.

Limitations

The present study has some limitations. First, the sample size may not have been adequate to detect significant changes in clinical outcomes between the experimental and sham groups. Second, cognitive performance was assessed using the in-game, pre-assessment program, which was performed prior to initiating the training program and after completion of the three-months training program. Third, the bug that was discovered in the Brain+ Alco-Recover application meant that two out of the four pre-specified cognitive domains had to be excluded. As a result, the cognitive assessment was reduced to only encompass processing speed, attention, and working memory. Fourth, the lack of a standardized assessment for the various cognitive domains meant that we were unable to detect potential far-transfer effects in cognition. The reliance on the in-game assessment of cognitive functions also precludes bold comparisons to the effects of other cognitive training programs that were assessed with standardized instruments, thus reducing the external validity of the present findings.

In addition, the development of the Brain+ Alco-Recover application was in its early stages, and as a result more complex features as well as adaptations of specific games were omitted. The lack of a notification system made it more difficult to remind the patients about their training sessions, and implementing such a feature should be emphasized in unguided training programs, as this could increase the number of completed games. Lastly, the sham group was not exposed to training that targeted verbal learning and episodic memory due to technical restraints making it impossible to cap the level of difficulty. This should be addressed in future versions of the Brain+ Alco-Recover application as well as any other cognitive training programs, since learning and memory have been implicated in alcohol-related disorders including patients with Wernicke-Korsakoff disorder [59,60], where it has been shown that memory functioning is less susceptible to the spontaneous recovery occurring with continuing abstinence [4].

Conclusions

The use of the Brain+ Alco-Recover serious gaming application was found to be a feasible and acceptable way of delivering cognitive training to patients with AUD in conjunction with conventional treatment. This early version of the training program showed a potential effect in improving both attention and working memory, which was possible even when the training sessions were performed at home with minimal to no support from a health professional. Further, the multi-domain cognitive training program could provide the means for reducing alcohol consumption and improving clinical outcomes. The demonstrated feasibility and acceptability of the Brain+ Alco-Recover application highlights that these promising results should be validated in a larger RCT, since uncovering an effective way of ameliorating cognitive dysfunctions and improving clinical outcomes is highly warranted for optimizing the future treatment for patients with AUD.

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Conflicts of Interest

The authors declare no conflicts of interest.

Abbreviations

ASI: Addiction Severity Index
AUD: alcohol use disorder
CI: confidence interval
DD: drinking days
HCL: highest craving level
HD: heavy drinking
HDD: heavy drinking days
ICD-10: International Classification of Diseases the 10th edition
ITT: intention-to-treat
MCL: mean craving level
MMSE: Mini-Mental State Examination
PP: per-protocol
PSA: processing speed and attention
RCT: randomized controlled trial
SD: standard deviation
SUD: substance use disorder
SUS: System Usability Scale
T: time point
TAU: treatment-as-usual
VAS: Visual Analogue Scale
WM: working memory

Multimedia Appendix 1

Multimedia appendices are supplementary files, such as a PowerPoint presentation of a conference talk about the study, additional screenshots of a website, mpeg/Quicktime video/audio files, Excel/Access/SAS/SPSS files containing original data (very long tables), and questionnaires. See https://jmir.zendesk.com/hc/en-us/articles/115003396688 for further information. Do not include copyrighted material unless you obtained written permission from the copyright holder, which should be uploaded together with your Publication Agreement form as supplementary file.

The Multimedia Appendices must be uploaded online, accompanied by a caption. CONSORT-EHEALTH checklists are always uploaded as Multimedia Appendices. Although this is primarily intended for randomized trials, the section of the checklist describing how an intervention should be reported

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Before submission, authors of RCTs must **fill in the electronic CONSORT-EHEALTH questionnaire at http://tinyurl.com/consort-ehealth-v1-6** with quotes from their manuscript (if you wish to comment on the importance of the items from the checklist for reporting, please also rate each item on a scale between 1-5). BEFORE you press submit, please generate a pdf of the form with your responses and upload this file as supplementary file entitled CONSORT-EHEALTH V1.6.

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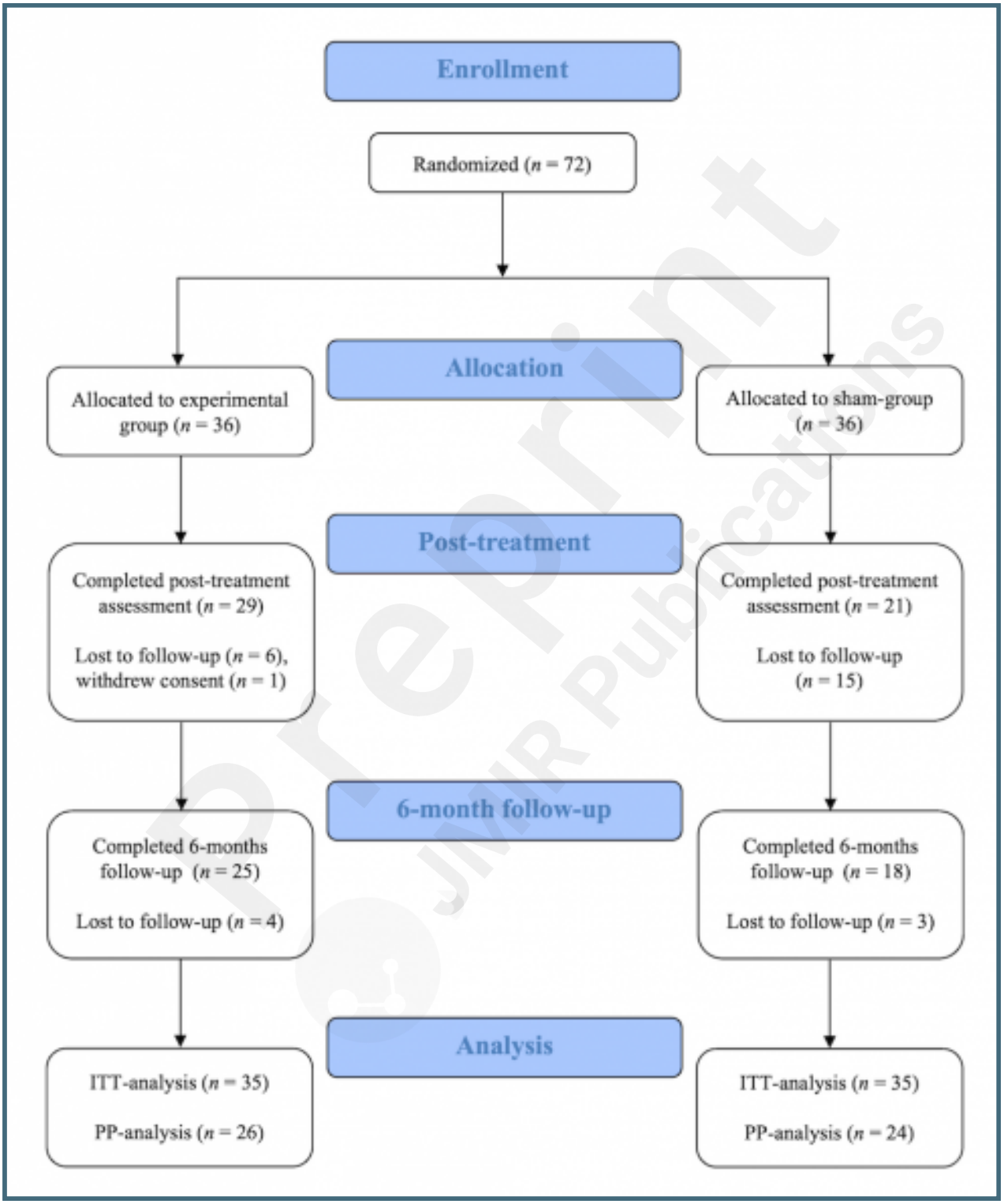
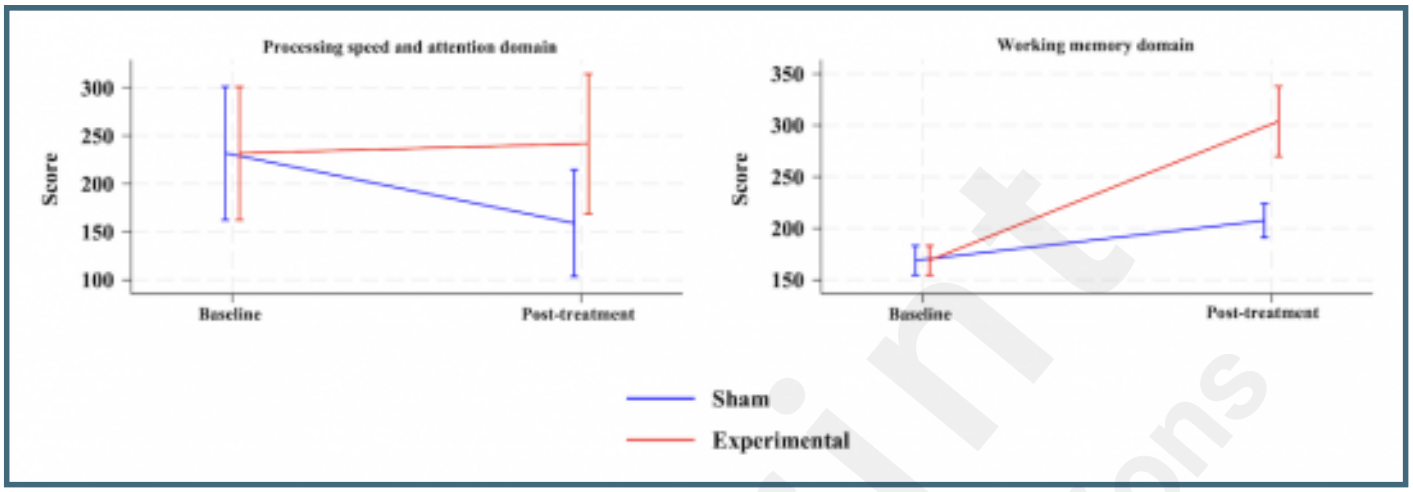
Supplementary Files

Figures

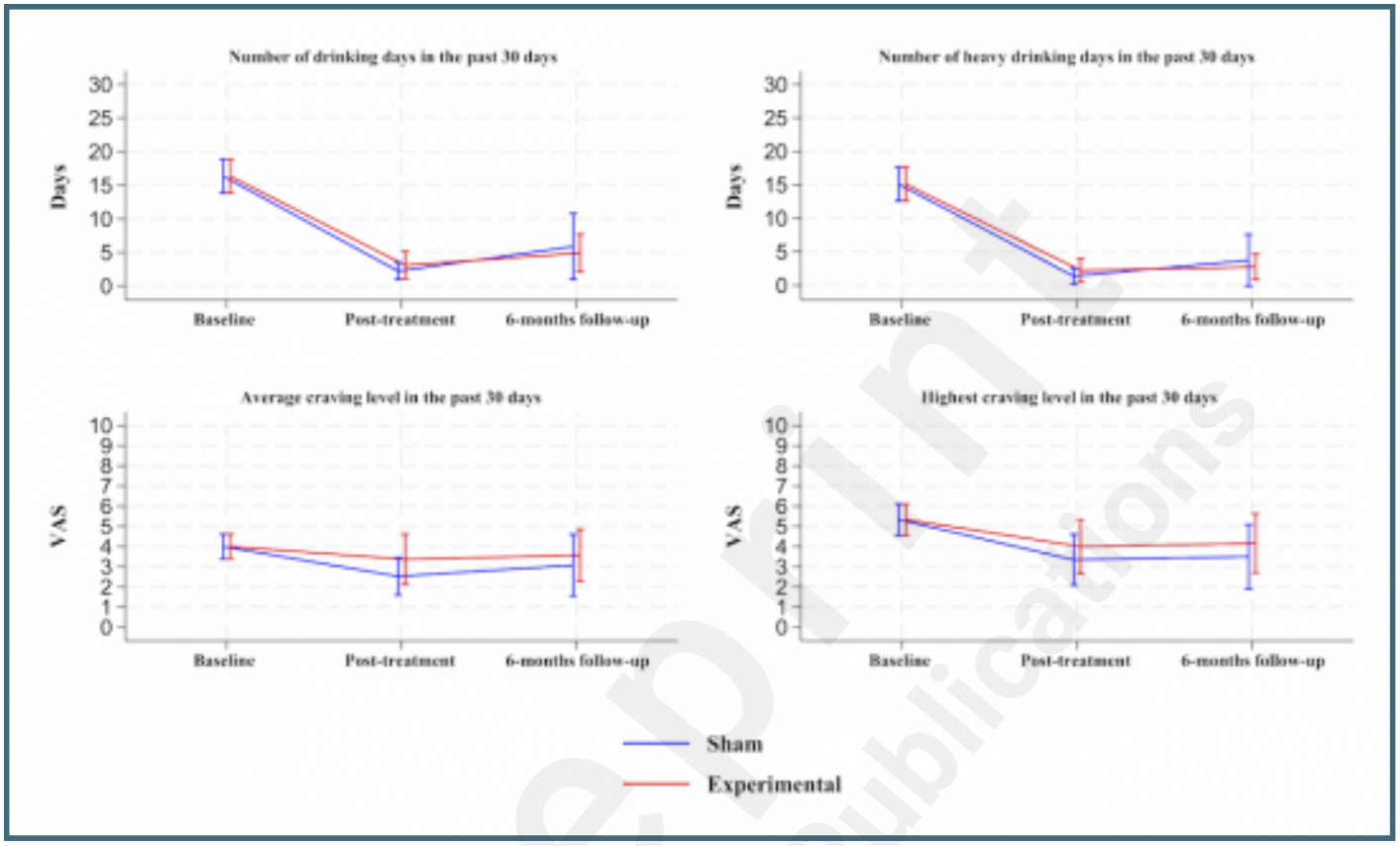
Adapted version of the CONSORT flow-chart diagram (Schulz et al., 2010). The ITT-analysis includes all the patients who were allocated to a treatment group, whereas the PP-analysis only includes the patients who reached the minimum of five completed game trials for each of the games in the Brain+ Alco-Recover application.



ITT-analyses showing the mean change scores in the processing speed and attention domain as well as working memory domain from the baseline assessment to the post-treatment measurement for the experimental group (red line) and the sham group (blue line). The abscissa indicates the measurement time points, and the ordinate indicates the mean composite brain score calculated from the performance on the individual games for each cognitive domain.



ITT-analyses showing the mean change in number of drinking days and heavy drinking days in the past 30 days as well as average and highest alcohol craving at baseline, post-treatment, and at 6-months follow-up for the experimental group and the sham group. The abscissa indicates the measurement time points, and the ordinate indicates either the number of days or mean total score on the VAS.



Multimedia Appendixes

Supplementary material including screenshots of the cognitive games from Brain+ Alco-Recover and supplementary tables S1 and S2.
URL: http://asset.jmir.pub/assets/89d474e3687e8b09283f7f6aa2f2b835.pdf

CONSORT (or other) checklists

CONSORT eHealth Form – the complete version, which is longer than the online form.
URL: http://asset.jmir.pub/assets/10f46eadf5647736e6a6aeae19db0078.pdf