Working Memory Training in Alcohol Use Disorder: A Randomized Controlled Trial
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Background: Alcohol use disorder (AUD) is associated with cognitive deficits such as impaired executive functions, which are hypothesized to contribute to the progression of the disease and worsen treatment outcome. Training of working memory (WM) to improve cognitive functions and thereby reduce alcohol use has been proposed as a novel treatment strategy.

Methods: Patients with AUD (n = 50) who were recruited to an outpatient addiction clinic were randomized to receive 5 weeks of active WM training or control training. Participants had weekly follow-up visits, and all cognitive training sessions were done online at home. Primary outcomes were WM function and change in self-reported heavy drinking. Secondary outcomes were craving, other drinking outcomes, and performance on a range of neuropsychological tasks from the Cambridge Neuropsychological Test Automated Battery.

Results: The active training group demonstrated a significantly greater improvement in verbal WM compared with the control group. No statistically significant effect of training was found on the primary drinking outcome, but a trend was observed indicating that WM training reduces the number of drinks per drinking occasion. WM training had no statistically significant effect on any of the other neuropsychological tasks.

Conclusions: Cognitive training can improve WM function in individuals with AUD, suggesting that such interventions are feasible to administer in this patient population. The results do not support an effect of WM training on heavy drinking or transfer effects to other cognitive domains. Future studies should evaluate WM training as an adjunct to evidence-based treatments for AUD to assess potential synergistic effects.

Key Words: Alcohol Use Disorder, Working Memory, Cognitive Training, Cogmed.

Individuals with alcohol use disorder (AUD) repeatedly choose actions that are obviously disadvantageous. An inability to control drinking, repeatedly relapsing, and continued drinking despite negative physical, psychological, and social consequences are not only the diagnostic criteria of the disorder (American Psychiatric Association, 2013), but may also be evidence of a disrupted ability to make rational decisions. This is in part explained by the fact that patients with AUD exhibit impairments across a wide range of cognitive domains (Stavro et al., 2013). It has been suggested that a novel strategy in the treatment of substance use disorders (SUDs) could be to reduce substance use via improvement in cognitive dysfunction, either through pharmacological (Sofuoglu, 2010) or behavioral interventions such as cognitive training (Bickel et al., 2014).

Executive functions (EFs) refer to several cognitive functions that allow individuals to self-regulate their behavior and select appropriate actions in accordance with their long-term goals (Diamond, 2013; Hofmann et al., 2012; Jurado and Rosselli, 2007). Working memory (WM), defined as the ability to maintain and manipulate information during a brief period of time, is a critical EF necessary for higher order self-regulation and decision making (Hofmann et al., 2012). There are several different theoretical models of WM, but one of the most influential models proposes that WM involves a central executive and 2 storage systems: the verbal WM (e.g., repeating a number sequence read aloud) and the visuospatial WM (e.g., remembering details/location of visual cues presented briefly on a screen; for more details, see Baddeley, 2003). Several lines of research have shown that AUD is associated with impairments in EF (for review, see Le Berre et al., 2017), including inhibition (Bjork et al., 2004; Finn et al., 2002; Lawrence et al., 2009a; Le Berre et al., 2012; Noël et al., 2012; Nowakowska-Domagała et al., 2012; O’Neill et al., 2006).
knowledge, no previous study has investigated the effects of WM training in patients with AUD.

The aim of the current study was to investigate the feasibility and efficacy of 5 consecutive weeks of computerized WM training on WM function and drinking in AUD patients. Furthermore, we wanted to investigate whether the hypothesized improvement in WM could induce transfer effects, that is, improvements in other EF related to impulsive behavior (e.g., response inhibition and risk taking), which was hypothesized to mediate the putative treatment effect on drinking behavior.

MATERIALS AND METHODS

Participants

Fifty patients with AUD currently not in any form of SUD treatment were recruited through public advertising. After an initial telephone screening, potential participants were invited to the Stockholm Centre for Dependence Disorders outpatient research clinic, where the study was performed. The study physician provided each participant with detailed information regarding the study procedure before written informed consent was collected. The study was approved by the regional ethical review board in Stockholm, was independently monitored by the Karolinska Trial Alliance (https://karolinskatrialliance.se/), and was conducted in accordance with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

The main inclusion criteria were as follows: male or female with 18 to 60 years of age; a minimum of 9 years of education; fulfilling the DSM-IV criteria for alcohol dependence; and having access to a home computer with an Internet connection. The main exclusion criteria were as follows: fulfilling DSM-IV criteria for current diagnosis of abuse or dependence other than alcohol (except nicotine); fulfilling DSM-IV criteria for any major psychiatric disorder (e.g., bipolar disorder, schizophrenia, or severe major depression); current suicidal ideation; severe somatic illness; and regular intake of psychotropic medications over the last 3 months, with the exception of selective serotonin re-uptake inhibitors for current anxiety or depressive disorders currently in remission. See Supplementary Information for a detailed description of all the inclusion and exclusion criteria.

Study Design

The study employed a randomized, controlled, double-blind design. Patients were randomized (1:1 allocation ratio) to 5 weeks of active WM training or control training. An external monitor from the Karolinska Trial Alliance created the randomization list together with Cogmed® without any involvement of any research staff. Each participant was asked to perform 5 training sessions per week, and the goal was to complete 25 training sessions in total. Participants were informed that they would earn 50 Swedish crowns ($5.75 USD) for each completed training session, but would receive compensation only if they completed at least 20 training sessions and the final test day. Included participants completed a baseline battery of neuropsychological tests at the clinic and thereafter returned on a weekly basis to report drinking, craving, and mood. The trial ended with a test day at the research clinic, which comprised end-of-study neuropsychological testing and compensation for participation. All participants were offered referral for treatment at Stockholm Center for Dependency
Disorder clinics. The primary outcome measures were heavy drinking and performance on Digit Span and Spatial Working Memory (SWM) tasks (see descriptions following).

Working Memory Training

The current study used Cogmed® software research version, which has been used in several previous studies (Klingberg et al., 2005; Rass et al., 2015) and consists of 12 different exercises of verbal and visuospatial WM. Each training session was composed of 8 exercises, of which 3 were present in all first 20 sessions, and the other 5 varied across sessions. The exercises performed at each of the first 20 sessions were grid, cube (remember sequences of visual stimuli on a grid and cube, respectively), and numbers (remember sequences of numbers read aloud). For further descriptions of the different Cogmed exercises, see the Supplementary Information. At inclusion, each participant was introduced to the software and provided with a unique login and password to use the software online at home. The participants were randomized to either active or control training, and the research staff and participants were blind to the allocation. The active training group performed 5 weeks of repeated adaptive cognitive training (5 sessions of 30 to 45 min/wk), in which the tasks become progressively more difficult based on the user’s performance. The control group, however, performed the same number of training tasks, but the training was nonadaptive (i.e., the number of items to remember in each trial was 2 to 3, and there was no increase in difficulty). In accordance with previous studies (Klingberg et al., 2005), the compliance to treatment was defined as completion of a minimum 20 training sessions during the 5-week study period. During the weekly visits, subjects also got feedback on how many trials they had completed, and encouragement to keep training. A research colleague not involved in the current study extracted information on the number of completed training sessions, without informing either the research subjects or the research staff of the treatment condition. Several measures were undertaken to minimize risk of unblinding. For instance, the randomization list was created by an external monitor, the brand name Cogmed® was never shown/mentioned to participants, and both participants and research staff were explicitly instructed not to discuss the content of the training during the weekly visits. For further details regarding blinding procedures, see the Supplementary Information.

Clinical Instruments

The psychiatric evaluation was performed by a study physician using the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 2000). Drinking outcomes were quantified by the Timeline Followback interview (Sobell and Sobell, 1992) at baseline and at the weekly visits. Heavy drinking days (HDD) were defined as a day with consumption of at least 4 or 5 standard drinks (equivalent to 12 g alcohol) for women and men, respectively. Craving at baseline and during the study was assessed using the Obsessive Compulsive Drinking Scale (Anton et al., 1995) and the Swedish shortened version of the Desire for Alcohol Questionnaire (Short-DAQ; Khemiri et al., 2017; Love et al., 1998), respectively. Mood was assessed using the Montgomery–Asberg Depression Self-Rating Scale (Swanborg and Asberg, 2001).

Tasks of Cognitive Function

All computerized tasks were from the Cambridge Neuropsychological Test Automated Battery (CANTAB®) and were administered using a touch-screen tablet PC (MOTION J3500-i7B) and press pad provided by Cambridge Cognition Ltd (www.cambridgecognition.com). For a detailed description of all tasks of cognitive function and their outcomes, see the Supplementary Information.

Digit Span Task. The Digit Span task from the Wechsler Adult Intelligence Scale-IV (Swedish version, 2010; Pearson assessment) was used to measure verbal WM. The participant is presented with digit sequences with increasing difficulty, and is asked to repeat each digit sequence. In the first part, participants are asked to repeat the digit sequence in the same order as presented (forward); in the second part, the digit sequences are reported in the opposite order (backward). The outcomes were total number of correctly reproduced digit sequences, as well as number of correct forward and backward digit sequences.

SWM Task. The SWM task from the CANTAB was used to assess visuospatial WM function (Owen et al., 1990). The participant is presented with a number of colored boxes on the screen and is asked to find blue tokens hidden inside these boxes and place them in an empty column on the side of the screen. Importantly, the participant is asked not to return to boxes where a token has been previously found. The outcomes were number of total errors, between-errors (opening a box in which a token has been found previously), within-errors (opening a box that has already been found to be empty), and a strategy score (number of times the participant begins a new search with a different box, indicating a poor choice of strategy).

Stop Signal Task. The Stop Signal Task from the CANTAB was used to measure response inhibition (i.e., the ability to inhibit a prepotent response; Logan et al., 1984). The main outcomes are the stop-signal reaction time (SSRT), the median reaction time of go trials, and the proportion of successful stops. See the Supplementary Information for further details.

Rapid Visual Processing. The Rapid Visual Processing (RVP) task from the CANTAB measures sustained attention (Coull et al., 1996; Kirby et al., 1999) is a task with the main outcomes are probability of hit, probability of false alarm, and mean latency. See the Supplementary Information for further details.

Cambridge Gambling Task. The Cambridge Gambling Task (CGT) from the CANTAB assesses decision making and risk taking (Rogers et al., 1999). The main outcomes are deliberation time, overall proportion bet, risk taking, and delay aversion. See the Supplementary Information for further details.

Stockings of Cambridge. The Stockings of Cambridge, a development of the Tower of London (Owen et al., 1990; Shallice, 1982), is a CANTAB test of planning and problem-solving ability. The main outcomes are mean number of moves and number of problems solved in a minimum of moves, for the most difficult problems (i.e., 5-move problems). See the Supplementary Information for further details.

Monetary Choice Questionnaire. The Monetary Choice Questionnaire (Kirby and Maraković, 1996; Kirby et al., 1999) is a task designed to estimate rates of delay discounting. It consists of 27 items that are presented as a choice between 2 different sums of money—either a smaller immediate reward or a larger delayed reward (e.g., “Would you...”). The rewards presented are small, medium, or large, and the time period varies across items. See the Supplementary Information for further details.

Statistical Analysis

Around the time the current study was planned, studies using Cogmed® WM training software had found effect sizes of Cohen’s d of approximately 1.0 for WM tasks (Klingberg, 2010). With a total sample size of 50, an alpha level at 0.05, and power 80%, the study was powered to detect large treatment effect sizes (i.e., Cohen’s...
completed the entire study (i.e., performed in inclusion). In the per-protocol (PP) analysis, only participants who compared to the baseline value (i.e., drinking the last 90 days before inclusion) were included. Missing data were imputed using baseline observations carried for intention-to-treat (ITT) analysis, all participants were included, and method, see Quisenberry et al., 2016; Snider et al., 2016). Using repeated-measures ANOVA for the whole study population or within treatment condition, respectively. Measurements of craving and mood were analyzed using mixed ANOVA with Treatment as the between-subject factor and Time (baseline, test day) as the within-subject factor. Significant main effects and interactions were further analyzed using Oldham’s correlation (the correlation between change score and mean of the baseline value for the 3 primary outcomes), by calculating Oldham’s correlation (e.g., symptoms of inattention; Spencer-Smith and Klingberg, 2015) and clinical outcomes such as drinking (Houben et al., 2015). There were no statistically significant differences in the full sample at inclusion (Table 1). In the study completers (PP sample), there were no significant differences between any of the baseline variables reported in Table 1 for the full sample, except for the number of drinks consumed in the last 90 days before inclusion, t(37) = 2.14, p = 0.039, indicating a higher consumption in the treatment group compared to the control group.

There was no difference between treatment groups regarding the percentage of study completers (treatment 76%; control 80%; χ²(1) = 0.117, p = 0.733). Of the 11 participants who did not complete the study protocol (i.e., failed to complete 20 training sessions), 5 of them still completed the follow-up visits including the test day. Of the remaining 6, 2 dropped out during the study and 4 dropped out immediately after inclusion and had no follow-up visits. No serious adverse events were reported in any of the treatment groups.

The ITT and PP analyses yielded similar conclusions for all outcomes; therefore, only results from the PP analysis are presented in the main article. The complete statistical analysis including full ITT analysis is found in the Supplementary Information.

**Working Memory**

For Digit Span total score, there was a main effect of Time, F(1, 37) = 11.30, p = 0.002, η² = 0.234, and no main effect of Treatment, F(1, 37) = 0.788, p = 0.380, η² = 0.021, but a significant Treatment × Time interaction, F(1, 37) = 6.12, p = 0.018, η² = 0.142. The interaction was driven by a significant improvement at test day compared with baseline only in the active training group, F(1, 18) = 14.41, p = 0.001, but not in the control group, F(1, 19) = 0.47, p = 0.50 (Fig. 2A). Similar results were found in the Digit Span backward score, with a significant main effect of Time, F(1, 37) = 8.60, p = 0.006, η² = 0.189, and no main effect of Treatment, F(1, 37) = 0.013, p = 0.911, η² = 0.00, but a significant Treatment × Time interaction, F(1, 37) = 6.14, p = 0.018, η² = 0.142 (Fig. 2B). For the forward score, however, there was a main effect of Time, F(1, 37) = 4.2, p = 0.047, η² = 0.102, but no significant main effect of Treatment, F(1, 37) = 2.21, p = 0.146, η² = 0.056, or interaction, F(1, 37) = 1.24, p = 0.273, η² = 0.032 (Fig. 2C).

For SWM total errors, there was no main effect of Time, F(1, 35) = 1.04, p = 0.316, η² = 0.029. Treatment, F(1, 35) = 0.003, p = 0.960, η² = 0.000, or Time × Treatment interaction, F(1, 35) = 0.057, p = 0.812, η² = 0.002. Similarly, no significant main effects or interactions were found for strategy score, between-error score, or within-error score (Fig. 3; see the Supplementary Information for full analysis).

**Drinking**

For the primary outcome of percent heavy drinking days, there was a significant effect of Time, F(1, 37) = 6.278, p = 0.017, η² = 0.145, indicating a general reduction over...
time (overall reduction from 53 to 45%), but no significant effect of Treatment, \( F(1, 37) = 1.82, p = 0.186, \eta_p^2 = 0.047 \), or Time × Treatment interaction, \( F(1, 37) = 2.257, p = 0.142, \eta_p^2 = 0.047 \) (Fig. 4A). For drinks per drinking days, there was no significant effect of Time, \( F(1, 37) = 1.850, p = 0.182, \eta_p^2 = 0.048 \), or Treatment, \( F(1, 37) = 1.732, p = 0.196, \eta_p^2 = 0.045 \), but a trend for the Time × Treatment interaction, \( F(1, 37) = 3.483, p = 0.070, \eta_p^2 = 0.086 \) (Fig. 4B). The active training group significantly reduced mean number of drinks per drinking days [baseline: 7.07 (2.80); study: 6.13 (2.46)], \( F(1, 18) = 4.574, p = 0.046 \), whereas no significant change was found in the control group [baseline: 5.58 (2.06); study: 5.73 (2.31)], \( F(1, 19) = 0.147, p = 0.706 \). No significant main effects or interactions were found for percent drinking days (Fig. 4C) or drinks per day (Fig. 4D). See the Supplementary Information for the full analysis.

**Craving and Mood**

For the Short-DAQ craving scale total score, there was a significant main effect of Time, \( F(3.6, 131.4) = 4.948, p = 0.002, \eta_p^2 = 0.118 \), indicating an overall reduction in craving (pairwise comparisons showed significantly lower craving score at each time point in weeks 1 to 5 compared with baseline; \( p = 0.01 \) to 0.03 for all time points; Fig. 5A), but no main effect of Treatment, \( F(1, 37) = 0.671, p = 0.418, \eta_p^2 = 0.018 \), or significant Treatment × Time interaction, \( F(3.6, 131.4) = 0.163, p = 0.944, \eta_p^2 = 0.004 \). Regarding Montgomery–Asberg Depression Self-Rating Scale total score, there was no significant main effect of Time, \( F(2, 74) = 1.544, p = 0.266, \eta_p^2 = 0.069 \), or significant Treatment × Time interaction, \( F(2, 74) = 0.888, p = 0.416, \eta_p^2 = 0.023 \) (Fig. 5B).

**Cognitive Functions**

Table 2 presents descriptive data, as well as \( p \)-value and effect sizes for the Treatment × Time interaction for all outcomes for the different tasks of cognitive function (see Table S1 for ITT analysis). In summary, no statistically significant treatment effect of WM training on any of the neuropsychological tasks (including delay discounting) was found (all Treatment × Time interaction terms \( p \)-value >0.1; see the Supplementary Information for full
statistical analyses). However, there were significant main effects of time for some cognitive task outcomes (e.g., SSRT), $F(1, 35) = 8.23, p = 0.007, \eta_p^2 = 0.190$, and RVP probability of hit, $F(1, 35) = 4.560, p = 0.04, \eta_p^2 = 0.115$, indicative of overall improvement in performance at test day compared with baseline. In contrast, for CGT, the significant main effects of time for overall proportion bet, $F(1, 35) = 6.688, p = 0.014, \eta_p^2 = 0.160$, and risk taking, $F(1, 35) = 9.642, p = 0.004, \eta_p^2 = 0.216$, indicated more impulsive behavior at test day.

**Subgroup Analysis**

In the subgroup analysis based on the median split of baseline levels of the primary outcomes (Digit Span total score; SWM total errors; percent heavy drinking), we did not find any significant Treatment × Time interactions for neither the low nor the high groups (all interaction terms $p$-value $>0.05$) for any of the outcomes. Further, in exploratory regression analyses investigating baseline outcomes as continuous variables rather than median split, similarly no significant interactions were found (all $p > 0.1$). Finally, in a separate post hoc rate dependence analysis, we calculated Oldham’s correlation and found no evidence of rate dependence for any primary outcome, with no correlations larger than 0.3 in the active treatment group (see the Supplementary Information for full statistical analysis).

**Cognitive Training Data**

There was no difference between treatment groups in mean number of completed training sessions overall [treatment 19.7; control 20.2; $t(48) = −0.194, p = 0.847$] or among study completers [treatment 23.8; control 23.7; $t(37) = 0.140, p = 0.889$].

The active treatment group exhibited a statistically significant training index improvement from baseline to test day, $F (1,18) = 169.91, p < 0.001, \eta_p^2 = 0.904$, accompanied by a significant increase in mean number of completed WM items over time, main effect: $F(24, 504) = 13.75, p < 0.0001, \eta_p^2 = 0.396$. As expected, the control group had a constant training index and number of completed items across the training sessions.

Within the active treatment group, there were positive correlations between improvement in training index and

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**Table 1. Sociodemographic and Clinical Characteristics of the Entire Sample of Study Participants at Baseline**

| Males/females | Active training | Control training |
|---------------|----------------|-----------------|
| 13/12         | 12/13          |

| Age | 49.6 (6.1) | 49.8 (8.7) |

| Education | Elementary school | High school | University/college |
|-----------|-------------------|-------------|-------------------|
|           | 4.0%              | 40.0%       | 56%               |

| Marital status | Never been married | Married/partner | Divorced | Widow | Daily nicotine use | Previous had treatment for AD | Age at first drink | Age when alcohol problem began | AD DSM-IV criteria | Heredity AD | OCDS total | TLFB 90 drinks | TLFB 90 drinking days | TLFB 90 heavy drinking days | TLFB 90 drinks per drinking day | Alcohol-free days before inclusion | Number of completed training sessions | Percentage of completers | Digit span total | Digit span forward | Digit span backward |
|----------------|-------------------|---------------|----------|-------|------------------|-----------------------------|-------------------|-----------------------------|------------------|-------------|------------|----------------|-------------------------|-----------------------------|--------------------------|-----------------------------|-----------------------------|------------------|-----------------|---------------------|
|                | 8%                | 76%           | 16%      | 0%    | 48%              | 40%                         | 13.9 (1.9)        | 34.0 (10.8)                 | 5.1 (1.2)        | 87%         | 22.7 (7.0) | 421.7 (211)   | 64.3 (21.6)      | 49.8 (28.2)                  | 6.5 (2.9)                    | 4.1 (2.7)                  | 19.7 (8.3)                  | 76%             | 15.7 (3.6)      | 9.8 (1.9)         | 5.9 (2.2)       |

Continuous outcomes are presented as mean (standard deviation). There were no statistically significant differences between groups on any of the outcomes.

AD: alcohol dependence; OCDS, obsessive-compulsive drinking scale; TLFB, Timeline Followback.

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**Fig. 2.** Digit Span scores at baseline and test day in participants who completed the study. The total score **(A)** and backward score **(B)** were significantly improved in the treatment group compared with controls. No statistically significant difference was found for the forward score **(C)**. Values are presented as mean ± standard error of the mean; * $p < 0.05$. 

For more details and statistical comparisons, please refer to the Supplementary Information.
improvement in Digit Span total score ($r = 0.548$, $p = 0.008$), Digit Span forward score ($r = 0.409$, $p = 0.058$), and Digit Span backward score ($r = 0.503$, $p = 0.017$).

**DISCUSSION**

The present study is, to our knowledge, the first randomized controlled trial investigating the effect of computerized WM training in a clinical sample of patients with AUD. The main finding was that WM training significantly improved verbal, but not spatial, WM function. No significant treatment effect was found on the primary drinking outcome of heavy drinking, whereas a trend was observed indicating that WM training may reduce the number of drinks per drinking day. No effect of WM training was found on craving, mood, or other cognitive functions. The WM training was a demanding intervention (5 sessions per week) and was administered online in the homes of the participants. Despite this, more than 75% of participants completed 20 sessions of cognitive training, and no adverse events were reported, suggesting that such a cost-effective intervention is feasible to administer in outpatient AUD patients.

Similar to previous studies in healthy control subjects (Dahlin et al., 2008; Jaeggi et al., 2008; Li et al., 2008) and other patient populations (Klingberg et al., 2005; Westerberg et al., 2007), the present study also found a statistically significant effect of repeated adaptive WM training on verbal WM capacity in AUD patients. Our results are also partly in line with the previous WM training studies indicating that WM training can improve WM function in alcohol dependence (Snider et al., 2018), heavy drinkers (Houben et al., 2011), and opioid use disorders (Rass et al., 2015). Similar to the current study, Rass and colleagues (2015) also found a significant effect of WM training on the Digit Span task manifested as improvement in backward score with no effect on forward score. Even though the Digit Span is widely used as a task of verbal WM function, it has been proposed that the backward task is a better measure of pure WM function, since it requires active manipulation of information (Gathercole et al., 2004). Within the active treatment group, we also found significant correlations between improvement in the training index and Digit Span score improvement, suggesting that the effect was mediated by the actual cognitive training performance. Taken together, our findings on WM outcomes partly corroborate previous research and further suggest that a clinical sample of AUD patients is receptive to targeted training of a specific cognitive domain such as verbal WM.

**Fig. 3.** Spatial Working Memory task performance in participants who completed the study. The main outcomes were total errors (A), strategy (B), between-errors (C), and within-errors (D) at baseline and test day for treatment and control groups. There were no significant differences between treatment groups. Values are presented as mean ± standard error of the mean.
In contrast to Rass and colleagues (2015), however, we did not find a significant effect on visuospatial WM. The reason for this discrepancy is not clear and was surprising given that the majority of Cogmed training exercises are visuospatial in nature. One possible explanation for our results is that the putative negative effects of alcohol use are more severe and
evident on visuospatial WM than verbal WM function, rendering the former more resistant to training for the time period observed in the present study. However, in a meta-analysis of cognitive deficits in AUD (Stavro et al., 2013), the overall effect sizes were in a similar range (approximately Cohen’s $d$ 0.35 to 0.55) with overlapping confidence intervals for all related constructs (i.e., WM [verbal], visuospatial, visual learning/memory, and verbal learning/memory). Furthermore, all these constructs were still impaired but had recovered to a similar degree in AUD patients with long-term abstinence (Cohen’s $d$ 0.20 to 0.25). This indicates that, in general, visuospatial WM is not more severely impaired or less prone to recovery than verbal WM in AUD patients and should therefore not explain our results. Another possibility is that our sample of AUD patients for some reason did not exhibit any impairments in SWM task performance, even at baseline. This is supported by the fact that there was no main effect of time (i.e., no significant change between baseline and test day) for any of the SWM task outcomes. Furthermore, in a previous study utilizing the same SWM task, Lawrence and colleagues (2009b) found that patients with alcohol dependence performed more errors (mean ± standard deviation [SD]: 40.3 ± 30.0) compared with healthy controls (22.8 ± 21.4), whose results on the other hand were in the same range as the AUD patients in the current study (25.2 ± 16.0). Taken together, the reason for lack of effect of WM training on visuospatial WM in our sample is not clear but can possibly be explained in part by lack of visuospatial WM impairment at baseline.

The neurobiological mechanism of the WM training in AUD patients is currently not known. Prior studies have indicated that WM training mainly affects the frontoparietal cortical regions responsible for both WM and attention (Constantinidis and Klingberg, 2016). Furthermore, positron-emission tomography neuroimaging studies have indicated that WM improvement through cognitive training is associated with changes in dopaminergic neurotransmission, affecting cortical D1 receptor density (McNab et al., 2009) and striatal dopamine release targeting D2 receptors (Bäckman et al., 2011). Since alcohol induces dopamine release (Boileau et al., 2003; Di Chiara and Imperato, 1988) and AUD patients exhibit dysregulated dopaminergic transmission in both the striatum (Heinz et al., 2005) and frontal cortex (Narendran et al., 2014), one might hypothesize that
AUD patients are resistant to dopamine-dependent WM training. However, our findings suggest that these dopamine-ergic deficits in AUD patients do not hinder verbal WM improvement. Furthermore, our results indicate that it is possible to improve AUD patient’s verbal WM capacity through repeated daily WM training, despite continued alcohol intake during the training period.

We found no statistically significant effect of WM training on self-reported drinking outcomes. It is possible that there is an actual treatment effect that we failed to detect because of lack of power given our limited sample size. This is supported by the fact that the mean reduction in HDD, even though not statistically significant, indeed was greater in the treatment group (−11.5%) compared with controls (−3.4%). Furthermore, there was a trend in the secondary outcome, drinks per drinking day, suggesting a putative treatment effect in favor of WM training compared with control training. Although speculative, this may indicate that any potential clinical effect of WM training on drinking could be via improvement in impulse control when the drinking behavior is initiated, but future studies are needed to confirm this tentative finding in experimental conditions or via real-time data collection. In contrast to our findings, a previous online study of heavy drinkers did find a significant effect of WM training on drinking outcomes (Houben et al., 2011).

It is thus possible that WM training has an effect on drinking behavior in individuals with less severe substance-related problems, whereas the effect is diminished in the more severe phenotype of AUD. Another possibility is that the putative benefits of WM training in AUD populations may be evident only if WM training is administered adjacent to evidence-based AUD treatments, which address coping with craving and other alcohol use behaviors.

The current study found no evidence of WM training improving other cognitive functions (i.e., transfer effects), as assessed by a wide range of neuropsychological tests. Previous research has been inconsistent to what degree WM training induces such transfer effects. Some studies have indeed found that WM training can improve attention (Bigorra et al., 2016; Brehmer et al., 2009; Conklin et al., 2015; Green et al., 2012; Klingberg et al., 2005) and general fluid intelligence (Au et al., 2015; Jaeggi et al., 2008). It is, however, important to note that there are several studies that have failed to detect such effects (e.g., Owen et al., 2010), and there is an ongoing scientific debate regarding this question with conflicting results in different meta-analyses (e.g., Au et al., 2015; Melby-Lervåg et al., 2016). To what degree WM training can induce transfer effects in AUD patients remains, at present, an open question since very few studies have been conducted thus far. Two studies in AUD patients have indicated WM training transfer effects through improvement in delay discounting (Bickel et al., 2011) and impulse control (Brooks et al., 2017). In a recent study in opioid-dependent patients, however, no transfer effects to other cognitive domains were found (Rass et al., 2015). This is line with the current findings, but some important considerations should be highlighted when interpreting these results. First, there was a significant main effect of time for some of the cognitive task outcomes, indicative of a spontaneous improvement in cognition or practice effects, which could conceal potential treatment effects. Second, it is possible that potential transfer effects are not possible to induce in AUD patients because of alcohol toxicity. Since acute alcohol intake impairs cognitive processes including memory function (e.g., Matthews and Silvers, 2004) and AUD is associated with widespread long-term cognitive deficits (Stavro et al., 2013), it is possible that neurotoxic effects of both acute (during the study) and long-term alcohol consumption diminish potential transfer effects to occur. Third, previous studies that did find transfer effects in AUD patients (Bickel et al., 2011; Brooks et al., 2017) were performed in an inpatient setting—suggesting that perhaps a controlled environment without substance intake is necessary for transfer effects to occur. Finally, it should be emphasized that the power of the present study to detect an effect with the Cohen’s d effect size of 0.4, as found for inattentive symptoms in previous studies on WM training transfer effects (Spencer-Smith and Klingberg, 2015), was only 28%. No definitive conclusions can therefore be made from the present negative finding.

There are several important limitations of the current study that are worth discussing. First, the sample size was limited, resulting in low power to detect medium-to-small effects. Furthermore, the follow-up time was too short to possibly elucidate long-term clinical benefits. Second, the AUD participants in the current study represent a subset of highly motivated patients. They are thus likely not representative of more clinically severe AUD patients, who may have more difficulties performing a demanding intervention such as 5 weeks of repeated cognitive training. Third, we did not include patients based on their baseline WM performance but rather on their DSM-IV criteria. In a subgroup analysis, however, we did not find any significant moderating effect of verbal WM, visuospatial WM, or heavy drinking on the primary outcomes. However, our power was small given the limited sample size, and a previous study with greater sample size did find that WM training effect in alcohol dependence is different depending on baseline performance (Snider et al., 2018). Thus, it is possible that interventions such as cognitive WM training may be clinically beneficial when targeted toward patients with existing deficits in WM function. Future studies should consider stratifying patients on baseline cognitive deficits to more clearly identify phenotypical differences in treatment response. Finally, an important limitation is that all cognitive training was performed at home and not in a controlled environment. We can, thus, not exclude that other people performed the actual training or that participants were intoxicated by alcohol during training, which of course could affect the outcome of WM training. Future studies should consider conducting the WM training supervised at the research clinic or collecting self-report data from participants on the training conditions if the training is done at home.
In summary, the current study showed preliminary data to suggest that it is possible to improve verbal WM function in AUD patients through repeated adaptive WM training performed online in the home environment. Our results did not however support an effect of WM training on drinking outcomes or transfer effects to improvement in other cognitive functions. Future studies should investigate whether administration of WM training as add-on treatment to evidence-based psychotherapeutic or pharmacological AUD treatments can improve treatment outcomes.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Supplementary Information.** Material and methods.

**Table S1.** Sociodemographic and clinical characteristics of study participants at baseline of subjects who completed the entire study protocol (PP analysis).

**Table S2.** Main outcomes of the tasks of cognitive functions at baseline and test day for each of the experimental conditions.