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Working memory training improves alcohol users' episodic future thinking: a rate dependent analysis

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Abstract

Background—Episodic thinking, whether past or future, uses similar neural machinery, and individuals with alcohol dependence have clear challenges with both. Moreover, alcohol dependents' narrowed temporal window likely increases greater valuation of immediate rewards. We aimed to strengthen working memory (WM) in alcohol dependent individuals and measure performance on near-transfer (novel WM task) and far-transfer delay discounting (DD) tasks, including episodic future thinking (EFT) performance. Importantly, heterogeneous intervention responses could obscure a treatment effect due individuals' baseline differences. Therefore, we consider WM, DD, and EFT DD scores using rate dependence analyses.

Methods—Fifty alcohol dependent individuals received either 20 active (Trained) or sham (Control) WM training sessions using the Cogmed© adaptive WM training program. Participants completed a near-transfer novel WM task, and far-transfer DD and EFT delay discounting tasks before and after training.

Results—Active WM training improved performance on near-transfer task. As determined by Oldham's correlation ($r_{mean(x,y),\ y-x}$), initially low near-transfer task scores improved more than initially high scores (i.e., rate dependence), in the Trained group only. Moreover, Trained group individuals with the highest rates of EFT DD at baseline rate-dependently decreased following training; whereas WM training had no effect on DD alone.

Conclusions—These data support the notion that WM training improves near-transfer task performance and may enhance the effects of EFT DD in a subset of alcohol dependents trapped within the narrowest temporal window. Rate dependent changes highlight that we should attend to baseline performance to better identify individuals most benefitted by an intervention.

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Keywords

working memory training; near-transfer; delay discounting; episodic future thinking; rate dependence; alcohol

Introduction

> "It's a poor sort of memory that only works backwards"
>
> – White Queen to Alice (L. Carroll, 1871)(1)

In this *Alice in Wonderland* quote, the White Queen curiously condescends Alice as if to say that her memory can do more than simply recall what she's done in the past. While seemingly as fantastical as the rest of the story, this line from Lewis Carroll is, in fact, correct. The neural machinery required to generate memories (i.e., episodic past thinking) considerably overlaps with that required to imagine the future (i.e., episodic future thinking). Moreover, both types of thinking utilize a combination of attention and working memory (2–5) to integrate information into plausible events, whether in the present or future (6–8). Therefore, in the words of Lewis Carroll, memory can indeed work forwards, *if* it is strong enough.

Individuals suffering from alcohol dependence have clear challenges with memory and and executive function (9–11). For example, drinking severity and magnitude of dependence is correlated with deficits in planning (12, 13) and when prompted, alcohol dependents produce significantly less specific contextual details when generating possible future events (14). Thus, if individuals with alcohol dependence are unable to efficiently plan for or imagine the future, one could argue they are trapped within a narrow temporal window (15). As a consequence, a narrow temporal horizon is hypothesized to give rise to greater valuation of immediate rewards such as alcoholic drinks, and the discounting of delayed rewards such as improved health and social relationships (16).

Episodic future thinking (EFT), a process that involves elaboration of future events (17), can decrease discounting rates of delayed rewards and indeed widen the temporal window in individuals suffering from alcohol dependence (15) and obesity (18–20). EFT requires individuals to construct and vividly imagine plausible positive future events at various time points (21, 22). Interestingly, participant working memory capacity was implicated in the EFT effect on delay discounting, where greater working memory capacity decreased discounting more compared to lower working memory capacity participants (21). Given the great overlap between memory and EFT, our hypothesis was that improvements in working memory would enhance the effect of EFT on delay discounting in individuals with alcohol dependence.

We have also shown previously that heterogeneous responses to an intervention, such as working memory training, can potentially obscure treatment effects due to differences in individuals' baselines (23–26). Therefore, we consider change scores in working memory performance delay discounting, and EFT delay discounting using rate dependence analyses, a method that considers individuals' change scores as a function of their own baseline.

Rate dependence is a phenomenon in which intervention response rates are differentially affected based on individuals' initial response rates (27, 28). Typically, rate dependence is demonstrated as an inverse relationship, wherein individuals with low baselines increase response rates following an intervention; and high baselines decrease, following the same intervention (27). Traditional rate dependent examinations correlate change in response rate with baseline responding. However, this methodology contains two mathematical biases, regression to the mean and mathematical coupling. For example, if change scores of any random x and y were correlated with x, a strong relationship of 0.71 emerges (29). Therefore, we determined the presence of a rate dependent-treatment effect using Oldham's method, to avoiding these biases, as described below and in detail in Snider et al.(25). Again, this method strengthens our analysis of the intervention effect by allowing us to consider each individual's treatment response as a function of their own baseline, providing the potential to identify a subset of individuals most-benefitted by these interventions.

Methods and Materials

Participants

A total of 50 participants completed a 20-session working memory training battery, and pre- and post- training assessments. All participants who reported drinking in the past six months and reported at least 3 of the 7 dependence criteria outlined in the DSM-IV-TR, were eligible. Participants were required to be 18–65 years of age, not pregnant or lactating, and not have any current significant medical or psychological disorders. History of stroke, seizures, loss of consciousness was exclusionary. Eligible participants were screened over the phone and/or in person. Informed consent was required from all participants. To determine whether the presence of alcohol, other drugs, or severe withdrawal may impair participants' ability to perform the behavioral tasks, participants provided breathalyzer and urine samples and completed a common sobriety test and withdrawal scale measure at every laboratory visit. All procedures were approved by the Virginia Tech Institutional Review Board.

Working Memory Training

Enrolled participants were randomly allocated to receive either 20 active (i.e., Trained group; n=25) or 20 control (i.e., Control group; n=25) working memory training sessions using the Cogmed© RM adaptive working memory training program. The Cogmed© RM working memory training paradigm was custom designed for the present study utilizing 12 unique working memory exercises. At each training visit, the program presented 10 of the 12 exercises in a rotating schedule to the participant. Each participant was assigned an individualized profile that recorded the highest level for each task on each day. Therefore, Trained participants began at the level from the previous day. Participants allocated to the Control group completed identical tasks as the Trained group. However, the difficulty level of all trials for each task/day was permanently set to 2 (i.e., very low). Therefore, Control group participants moved through the tasks, but did not progress to more difficult levels. Small monetary bonus payments were available at each training visit for the Trained group based on performance improvements. Each Control participant was yoked to a Trained participant to receive non-contingent bonus payments. Neither group was informed which group they were a part of. All Cogmed© logos were removed from the training environment to prevent participant bias. The Cogmed© RM tasks were computerized robot-themed exercises that included a heterogeneous mixture of visuospatial and verbal working memory tasks, including tasks that required both. Cogmed© and Cogmed© working memory training are trademarks, in the U.S. and/or other countries, of Pearson Education, Inc. or its affiliate(s).

Near-transfer Task – Following Instructions

Prior to and following training (pre- and post-assessments), participants completed a visuospatial and verbal working memory task, called "Following-Instructions" by Cogmed©**,** that was not trained, but was similar to the training tasks, to measure near-transfer effects of working memory training. During this task, a desktop was displayed with a variety of stationary items, such as colored boxes and bags, crayons, tape dispensers, erasers, etc. Participants were asked to listen to a series of verbal commands and then carry them out using the cursor. For example, the commands might have said, "click on the red eraser; drag the green tape to the blue bag; put the yellow crayon in the green box". The participant was required to wait until the list of commands was completed prior to beginning the list of movements. Participant scores were calculated based on the number of commands completed correctly (and in the correct order) across multiple trials. Research staff administering these and the other assessment tasks (described below) were blinded to the participant's group assignment.

Far-transfer Task – Delay Discounting Alone

Participants also completed two types of the delay discounting task at the pre- and post-assessment sessions. First, the delay discounting task was administered alone to demonstrate the effects of working memory training on delay discounting. The delay discounting task, an adjusting amount procedure, systematically titrated the immediately available amount to determine indifference points to a delayed $1000 at each of the 5 delays (30). Mazur's hyperbolic equation (31) was fit to these points to calculate discounting rates (i.e., k).

Far-transfer Task - Episodic Future Thinking Cue Generation and Discounting Task

Participants also completed episodic future thinking (EFT) delay discounting. EFT cue generation was completed via research staff interview. As described in detail in Snider et al. (15), participants were asked to vividly describe positive events that could realistically occur at future time-points that matched the delays in the discounting task (i.e., 1 day, 1 week, 1 month, 3 months, 1 year). Following the interview, participants completed an EFT delay discounting task during which their individually generated episodic cues were presented on the screen. Again, the delay discounting task systematically titrated the immediately available amount to determine indifference points to a delayed $1000 at each of the 5 delays (30) and Mazur's hyperbolic equation (31) was fit to the indifference points.

Alcohol Use Disorders Identification Test (AUDIT) - Modified

Alcohol misuse and severity was assessed at pre and post assessment visits using the 10-question AUDIT questionnaire (32). Of note, the instructions were modified from asking about participant “past year” drinking to asking about “current” drinking behavior. This change was made to allow for differences in completion rates and be sensitive enough to capture a change in drinking severity between pre and post training.

Data Analysis

Change scores from baseline were calculated for the near-transfer (Following Instructions), far-transfer (delay discounting and EFT delay discounting), and AUDIT tasks for both training groups. Working memory group mean change scores were then compared using a simple unpaired t-test. Six participants were excluded from the delay discounting alone analyses due to a lack of systematic delay discounting (i.e., Criterion 2) (33). A total of 6 participants did not complete the EFT delay discounting task because the task was added to the study after it began. An additional 3 participants who completed the task were excluded from analysis for multiple occurrences of a >20% increase in indifference point for the delayed magnitude compared to the immediately preceding indifference point (33) (ie., jumping; Criterion 1). *Calculating Rate Dependence.* Oldham’s correlation was used to determine the presence of a rate dependent effect of the WM on all of the measures. Oldham’s correlation is proposed to more accurately test for rate dependency because it removes the mathematical biases, mathematical coupling and regression to the mean, inherent in the traditionally used rate dependent correlation (23–25, 34).

Oldham’s correlation is:

$$Corr\left((x-y), \frac{(x+y)}{2}\right) = \frac{\mathrm{S}^2{}_{\mathrm{x}} - \mathrm{S}^2{}_{\mathrm{y}}}{\sqrt{(\mathrm{S}^2{}_{\mathrm{x}} + \mathrm{S}^2{}_{\mathrm{y}})^2 - 4r^2{}_{\mathrm{xy}}\mathrm{S}^2{}_{\mathrm{x}}\mathrm{S}^2{}_{\mathrm{y}}}}$$

where x is the baseline measure, y is the post-treatment measure, $s^2{}_x$ is the variance of x, and $s^2{}_y$ is the variance of y. The correlation between x and y is $r_{xy(34)}$. More simply, Oldham’s correlation is the correlation between the change of x and y and the average of xy ($r_{mean(x,y),\ y-x}$). To assess the near-transfer and far-transfer DD alone task for rate dependence, a Pearson correlation was utilized. In contrast, for the far-transfer EFT DD and AUDIT tasks, a Spearman correlation was utilized because the residuals were non-normally distributed. As described in Snider et al.(25) and Quisenberry et al.(24), correlations of >0.3 demonstrate a moderate effect size and has been used previously to indicate the presence of rate dependent effects of an intervention (23, 35).

Results

Demographics

Table 1 reports the group demographics separated by working memory training group. No significant differences in any demographic variables were present between the groups. Our modified AUDIT score changes between pre- and post-assessments did not differ between the groups (p>0.05), nor did they engender a rate dependent effect (r<0.30). When correlating income, education, age, or AUDIT with change in WM score or EFT DD, only one significant correlation emerged. Income was positively correlated with changes in EFT DD between S1 and S4 in the Trained group such that delay discounting rates decreased the most in those with the lowest incomes. However, when rate dependence analyses were run controlling for income, Oldham's correlation remained above the 0.30 benchmark (r = 0.34) for the Trained group and below the benchmark (r = −0.15) for the Control group.

The present study was designed as a use-inspired basic research study (Pasteur's quadrant) (36) bridging the gap between basic and applied research. As such, our goal was to understand the mechanisms that support the outcomes of particular interventions, and was not originally conceptualized as a clinical trial. The primary outcome was to demonstrate differences between the working memory training groups on working memory task performance, delay discounting rate, and episodic future discounting rate. The secondary outcome was demonstrating differences of rate dependence between training groups on these measures. Figure 1 shows the CONSORT chart beginning at the time of enrollment, marked by the signing of the informed consent document. Note that this study is not registered on clinicaltrials.gov.

Working Memory

Figure 2A depicts the proportion of change in near-transfer task scores from pre to post training between training groups. A significant difference was obtained in this change between groups $t(48)=2.65$, $p=0.011$, where the Trained group improved significantly more than the Control group.

Figure 2B represents the traditional depiction of rate dependence in which the proportion of change from pre-training is plotted as a function of the pre-training near-transfer task scores. The linear regression line is included to help the reader visualize the direction of the relationship. Rate dependence was determined using Oldham's correlation (described above). The correlation between change from pre- to post-training and the average of pre and post assessment scores determined a rate dependent relationship for the Trained group (r= −0.36), but not for the Control group (r= −0.18).

Delay Discounting Alone

Changes between pre- and post- assessment delay discounting rate did not differ between working memory training groups (p=0.33). Discounting rates also did not change rate dependently in either group (Oldham's correlation: Trained group r = 0.23; Control group r = −0.05).

Effects of Episodic Future Thinking on Delay Discounting

Figure 3A demonstrates the change in EFT delay discounting rates (i.e., $\ln k$) between pre- and post- assessments. No significant difference was detected between working memory training groups at the group mean level (p = 0.295). However, Figure 3B illustrates the traditional representations of change scores plotted as a function of pre-training discounting rates. When analyzed using Oldham's correlation, only the Trained group demonstrated a rate dependent relationship of change in EFT delay discounting rate as a function of baseline EFT discounting rate (r= −0.39), whereas the Control group did not (r = −0.15).

Discussion

The data presented here suggest four important new developments for our field: 1) adaptive Cogmed© working memory training regimens (i.e., Trained group), compared to sham training (i.e., Control group) improved performance on a similar, but non-trained, task (near-transfer Following-Instructions task) in individuals with alcohol dependence, 2) individuals in the Trained group with initially low near-transfer task scores improved more than those with initially high scores (i.e., rate dependence), 3) rates of delay discounting-alone did not significantly change between training groups, nor was it rate dependent, however 4) individuals with the highest rates of EFT delay discounting at baseline rate-dependently decreased the most following an EFT intervention, but again only in those who completed the active working memory training regimen. Therefore, while working memory training does not affect delay discounting directly, it may enhance the effectiveness of EFT in a subset of alcohol dependent individuals; perhaps by strengthening their ability to reconstruct the cues during the task (see below). The following discussion expands upon these findings and corroborates them with the previous literature. We conclude with a consideration of the potential mechanism by which working memory training may contribute to the effect of EFT on delay discounting.

Working memory is an executive process that involves both temporarily storing and manipulating incoming information (37), requiring both short term memory capacity and attention to carry out complex tasks under increased cognitive load situations (5, 38). In the past 15 years, “brain-training”, a mass marketing of commercial games and products, have touted that they can improve consumers’ working memory and cognitive ability in daily activities. These programs generally include a combination of both visuospatial and verbal short-term and working memory tasks that adaptively respond to individuals’ performance.

The literature has investigated whether these training paradigms can improve working memory scores on related tasks. For example, Cogmed© working memory training improved near-transfer tasks scores (working memory and following-instructions), and math scores in children (ages 7–15) with ADHD (39). Cogmed© training also significantly improved near-transfer performance in methadone maintenance patients (40), and sustained attention in a far-transfer tasks (tasks much different from those trained) in healthy young (ages 20–30) and older adults (60–70), compared to non-trained individuals (41). Of note, while meta-analyses report that near-transfer task performance shows small magnitude improvements, this improvement is not associated with improved clinical outcomes (42–44). Far-transfer tasks have greater potential for producing clinically relevant outcomes, however performance improvements are even more limited or have not been demonstrated at all (45, 46). These empirical findings are consistent with a meta-analysis and review of this literature, reporting that working memory training seems to improve performance on trained tasks and, to some degree, near-transfer tasks. However, these reviews found very little evidence that working memory training transfers to far-transfer tasks and/or cognitive function defined broadly (47, 48). Given that the Cogmed’s© Following-Instructions task in the present study, a near-transfer task, included both visuospatial and verbal working memory components (components both trained in the high dose group), we demonstrated consistency with the near-transfer literature.

Interestingly, although the effects of working memory training on far-transfer effects have been weakly supported, the effect of an intervention can be lost within heterogeneous changes from baseline scores (23–25). That is, individuals may be differentially affected by a particular intervention (increasing initially low rates or decreasing initially high rates) dependent on baseline performance. In fact, when we employed Oldham's method for determining rate dependent relationship, we found rate dependence in 67% of conditions examined, in which stimulant interventions differentially affected responding on impulsivity tasks in both preclinical and clinical populations (23). This demonstration highlights rate dependence as a robust phenomenon that should be examined in intervention research. Therefore, we hypothesized working memory transfer effects, whether near or far-transfer should also be assessed by examining rate dependence to avoid obscuring the intervention's effects. Indeed, in the present study the actively Trained working memory group rate dependently improved near-transfer (i.e., Following-Instructions) and the combined far-transfer (EFT delay discounting) task performance, but not delay discounting alone nor modified AUDIT scores.

Delay discounting alone was hypothesized to have differential improvement following working memory training, however, this was not demonstrated. Instead, the combination of working memory training and EFT improved (i.e., reduced) delay discounting rates to a greater extent in those with the highest initial rates, suggesting a combination effect of these two interventions. This suggestion is bolstered by the demonstration that EFT did not decrease EFT delay discounting in the absence of working memory training (i.e., Control group).

Episodic Future Thinking is the process of vividly pre-experiencing an event or situation (17). Given the overlap between EFT and working memory processes (as described above), the present study sought to support the notion that individuals who strengthen their working memory capacity may enhance their episodic future thinking performance thereby increasing EFT's effect on delay discounting (i.e., far-transfer effect). Consistent with the far-transfer literature, we did not find a group effect of working memory training on EFT delay discounting. Instead, an examination of the individual's change from their own baseline revealed a rate dependent effect of active working memory training on EFT delay discounting. That is, individuals from the Trained group who began training with the highest discounting rates, decreased their discounting rates the most following EFT. These results suggest that individuals trapped within the narrowest temporal window (i.e., greatest discounting of delayed rewards) may demonstrate far-transfer effects, and be benefitted by working memory training to widen their temporal horizon. We note, that we do not intend to imply that these results are sufficient to propose the two intervention types as a validated precision approach to alcohol use disorder, but instead a potential viable avenue for future research and iteration. The purpose of this manuscript was to highlight the value of utilizing Oldham's correlation as a tool to evaluate pre/post intervention data from a different perspective (i.e., individual baseline differences) than is typically used in human studies. That is, using this methodology we uncovered a relationship between working memory and episodic future thinking that would have otherwise gone unnoticed. These results are the first indicators this relationship should be further explored.

While the mechanism behind these findings is unknown, a brief review of the research may help to shed some light on a potential interpretation. As described above, individuals suffering from alcohol dependence are deficient in working memory tasks (9) and demonstrate deficits in planning for the future (12). Moreover, individuals with alcohol dependences demonstrate other executive function deficits including delay discounting contributing to poor self control (49).

Previous work has demonstrated that these deficits may be at least partially overcome to improve decision-making. For example, working memory training improved working memory (same task as training) and reduced alcohol drink intake by alcohol dependent individuals (10); and reduced delay discounting among stimulant users (50). Moreover, imagining the future improved prospective memory in drinkers (12, 13) and in healthy volunteers following acute alcohol administration (51). Importantly, engaging in EFT has been demonstrated to reduce delay discounting in a variety of populations, including individuals suffering from alcohol dependence (15, 18–20, 22, 52). Moreover, the reductions in delay discounting rates were most robust in those with higher working memory (21), suggesting that the mechanism through which working memory and EFT reduce delay discounting overlap.

In the year 2000, Baddeley added the episodic buffer to his model of working memory (53). The episodic buffer works to integrate and provide temporary storage for episodic units. Consistent with this model, episodic memory (and buffering) is necessary for generation of plausible future episodes (6), likely because past and future episodes are reconstructed each time they are re-imagined (3). Uniformly, working memory capacity contributed to the construction of episodic future thoughts in college students (8) and working memory training improved episodic memory in older adults (~70 years old) (54) highlighting the extensive integration of working memory and prospective function. Therefore, given this overlap between the processes of working memory and episodic future thinking, the present results suggest that working memory training increases the participants' capacity to regenerate their episodic future cue each time they are presented with the cue during the delay discounting task. This enhanced regeneration, through the episodic buffer, is hypothesized to super-charge the effects of EFT to benefit individuals with the narrowest temporal window. Future research specifically designed to examine the associated neural processes is warranted.

Although the modified AUDIT did not change following the working memory training, nor were the results rate dependent, these scores do not demonstrate the clinical impact of the combination intervention of working memory training and EFT on self-reported AUDIT. The modified AUDIT measures were collected prior to the generating EFT cues at the post-assessment visit. Therefore, these scores measured the effect of working memory training only, and not the impact of the combination. Future studies designed to explicitly measure the impact of the combination of working memory and EFT, including the impact on a biological level (i.e., via neuro-imaging) are viable next steps in this line of research.

Conclusion

The extant literature on working memory training exhibits strong evidence for enhancing working memory performance of tasks similar to those trained; however, evidence that working memory training enhances performance on tasks much different from those trained is harder to demonstrate. Here we suggest that a closer examination of individual's performance compared to their own baselines, reveals a rate dependent far-transfer effect of adaptive working memory training on an already powerful intervention, episodic future thinking. Moreover, given the extensive overlap, neurologically and behaviorally, between working memory and episodic future thinking, these two processes provide a promising and novel combined adjunctive therapy option for individuals trapped within the narrowest temporal window. In sum, and in reference to the White Queen's comment to Alice in Wonderland, memories can work forwards and working memory training can help you remember the future.

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1. Drug & Alcohol Dependence. 2017; Abstract #193. "The worse get better: Instruction following improves among the alcohol dependent rate dependently" by S.E. Snider, S.M. LaConte, W.K. Bickel.
2. Alcoholism Clinical and Experimental Research. 2016; Abstract #438. "Remember To Think Ahead: Working Memory Training Improves Episodic Future Thinking Rate Dependently In Alcohol-Dependents" by S.E. Snider, S.M. LaConte, W.K. Bickel.

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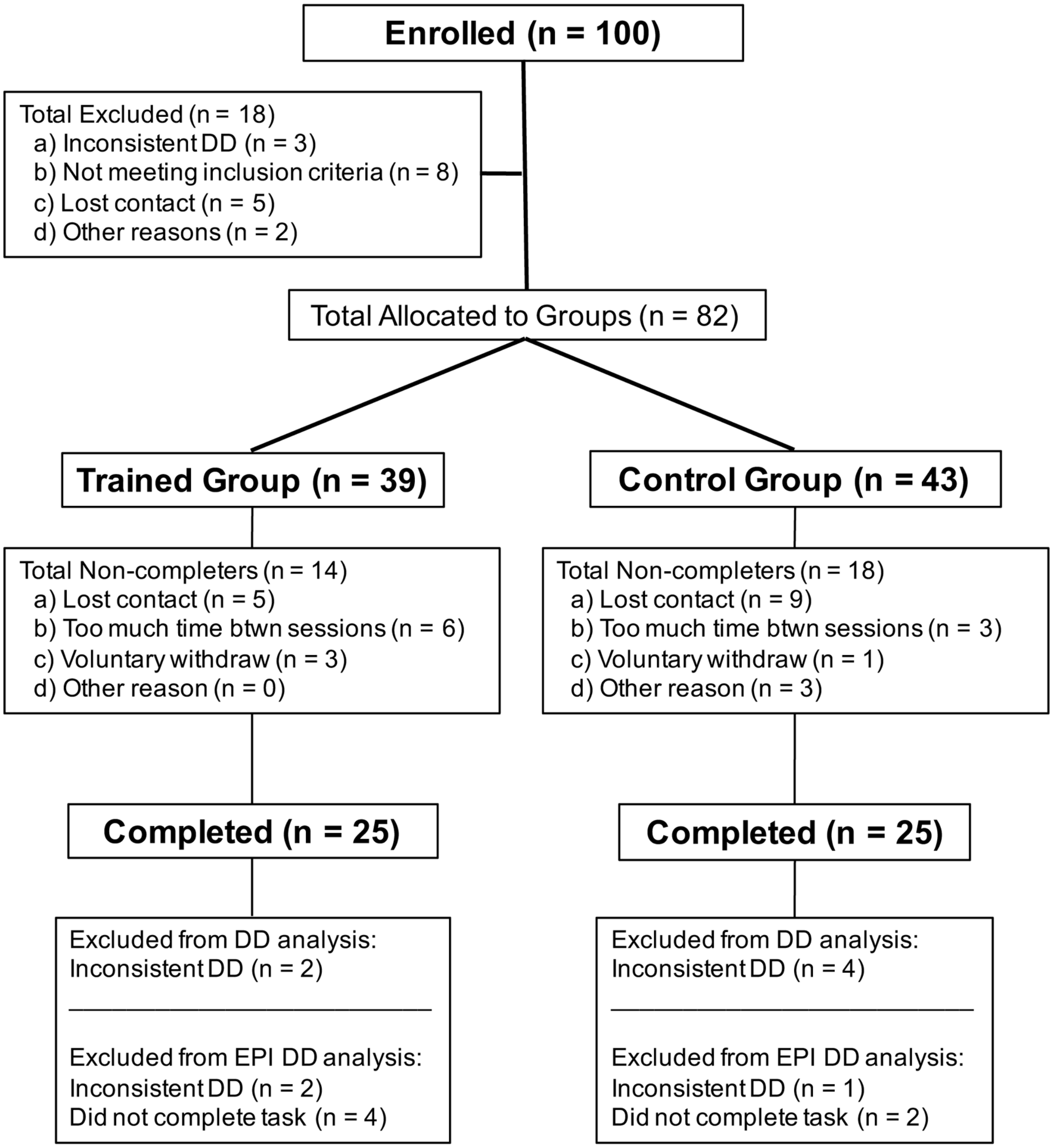

Figure 1.
Consolidated Standards of Reporting Trials (CONSORT) chart represents the flow of participant allocation and completion, including the number of participants and reasons for non-completion. Delay Discounting is abbreviated “DD” within the chart.

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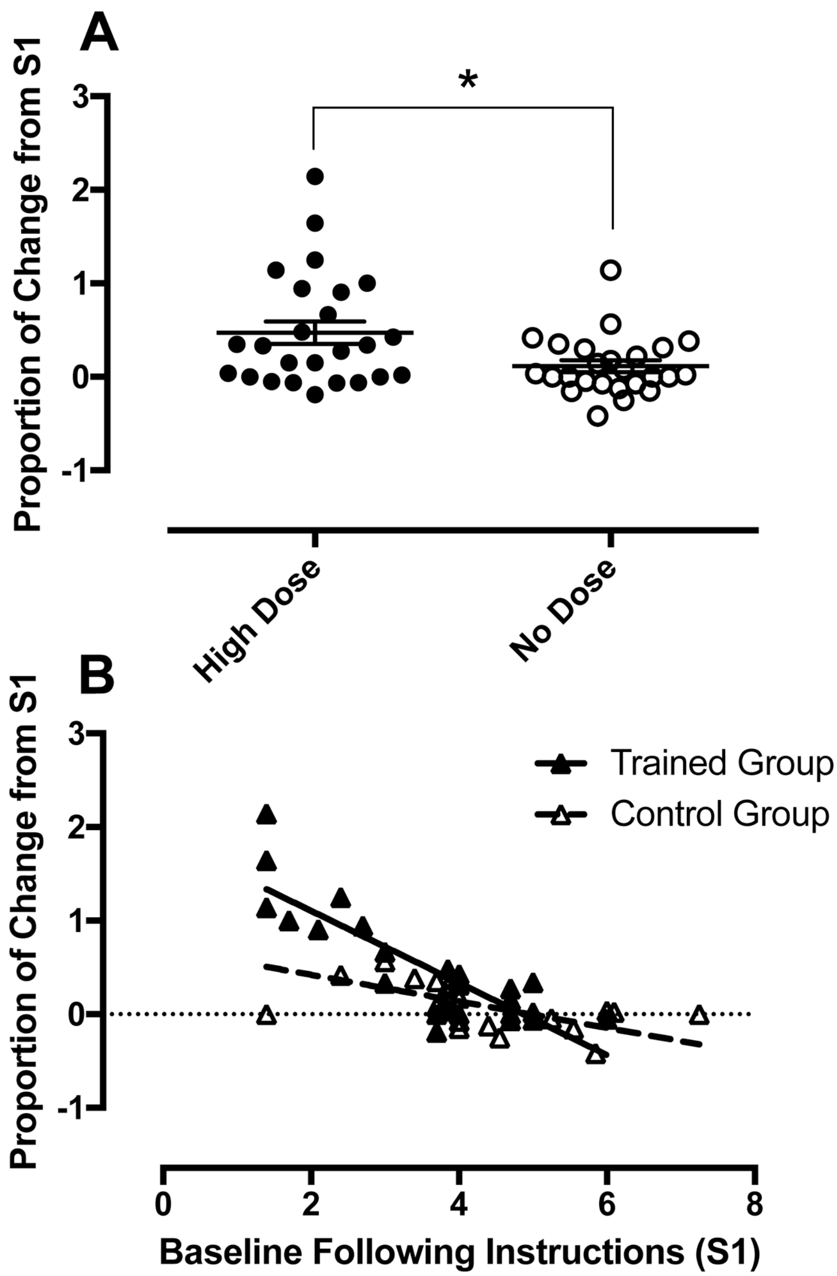

Figure 2.

Working memory training effects on near-transfer task performance. Panel A: Proportion of change in near-transfer task scores from baseline between Trained and Control groups. Horizon lines indicate group means ±SEM. Panel B: Depicts the traditional method for representing proportion of change from baseline plotted as a function of baseline near-transfer task scores. Note: the presence of rate dependence was determined using Oldham's correlation (see text). *p<0.05.

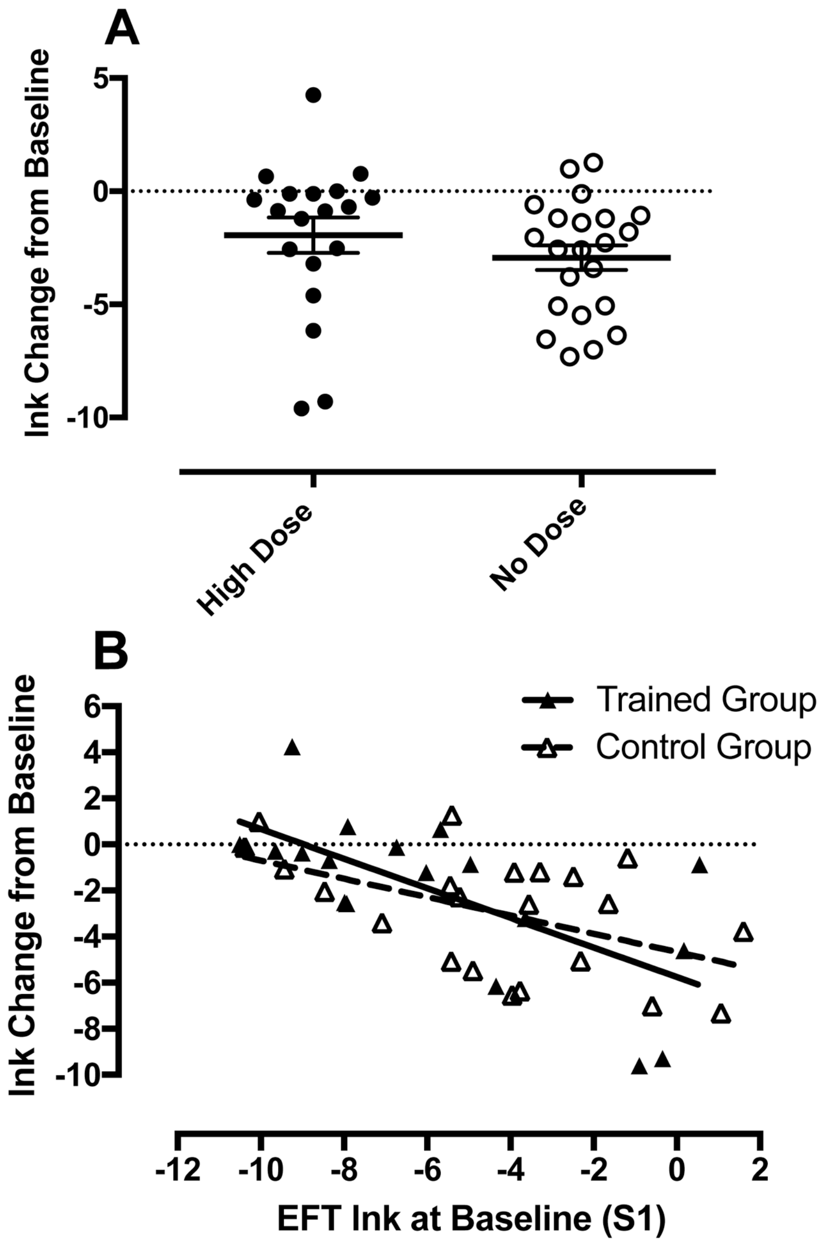

Figure 3.

Working memory training effects on Episodic Future Thinking (EFT) delay discounting. Panel A: Change in EFT delay discounting from baseline EFT delay discounting between the Trained and Control groups. Horizon lines indicate group means ±SEM. Panel B: Depicts the traditional method for representing change from baseline plotted as a function of baseline EFT delay discounting ln*k*. Note: the presence of rate dependence was determined using Oldham's correlation. *p<0.05.

Table 1

Demographics between high and no dose working memory training groups. No significant differences between groups.

WM Training Group	Gender (% Male)	Race (% Caucasian)	Age (Years)	Education (Years)	Monthly Income ($)
Trained	68%	64%	42.5 (2.0)	13.5 (0.4)	749.3 (215.4)
Control	88%	52%	42.4 (2.3)	12.6 (0.4)	576.4 (142.3)