APPLICATION OF NEW TECHNOLOGIES IN THE TREATMENT OF SUBSTANCE USE DISORDERS

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APPLICATION OF NEW TECHNOLOGIES IN THE TREATMENT OF SUBSTANCE USE DISORDERS

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EDITORIAL
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Editorial: Application of New Technologies in the Treatment of Substance Use Disorders

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Keywords: new technologies, tobacco use disorder, transcranial magnetic stimulation, substance use disorder, smartphone application, working memory

Editorial on the Research Topic

Application of New Technologies in the Treatment of Substance Use Disorders

Substance use disorders (SUDs)—a social, economic, and medical burden—are a global problem. Over time, the number of people with SUDs has increased significantly. SUDs are usually resolved with psychotherapy, but when necessary, pharmacotherapy is also required. Most of the time, however, these methods are not always effective and this poses a significant challenge for developing more effective therapies. As technology advances, it brings new hope for the treatment of SUDs.

Bu et al. found that the low-theta coherence network could significantly predict changes in individuals' cigarette cravings. Thus, the low-theta EEG coherence network in smokers' brains might be a biomarker of smoking cue reactivity and predict addiction behavior.

Tobacco use disorder (TUD) is currently treated with nicotine replacement therapy. This treatment is effective, but relapses are common, especially in the face of various TUD cue stimuli. In their case report, Peechatka et al. found that nicotine replacement therapy, coupled with nicotine free electronic cigarette use, was a promising option in preventing the relapse of TUD. However, these results are yet to be validated by a large randomized controlled study.

Transcranial magnetic stimulation (TMS), a new technology developed in recent years, has been widely used to treat mental illness. Studies have shown that repeated TMS is equally useful for treating SUDs (1). Newman-Norlund et al. found that theta-burst repeated TMS to the inferior frontal gyrus promotes nicotine addiction inhibitory control.

In recent years, the number of people with methamphetamine use disorders (MUD) in China has increased annually (2). The proportion of people with MUD has surpassed that of users of traditional drugs such as heroin. The treatment of MUD is also a significant challenge for the Chinese government. Wang et al. proposed a new approach for the treatment of MUD; they aimed to test the efficacy of paliperidone extended-release in decreasing methamphetamine use and reducing psychotic symptoms in methamphetamine-dependent patients after detoxification. Paliperidone administration resulted in a better retention rate and lowered psychotic symptom relapse among patients with psychotic disorders using methamphetamine. Based on more evidence from clinical studies, paliperidone, an antipsychotic, may be used to treat MUD in people with concomitant psychotic disorder in the future. Chen et al. have suggested psychological treatment for SUDs, using an autonomic progress bar to motivate. Their study's novel progress-bar tool effectively motivated treatment completion. It was also effective in forecasting continually negative urine test results. The tool's free open-source code makes it easy to implement in many substance-treatment services.

The increasing use of smartphones has accelerated the development and research of mobile phone-based interventions for SUD therapy (3–5). Smartphone applications offer various features

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with advanced software capabilities that can enhance chronic disease management. Clinical studies have increasingly examined whether smartphone applications can offer effective intervention in alcohol use disorders (AUD). Berman et al. conducted a pilot randomized controlled trial to evaluate the clinical impact of TeleCoach^{TM}, a web-based skills training smartphone application, on adult participants with AUD recruited from the internet in Sweden. After a 6-week intervention, there were significant within-group effects on alcohol consumption, but there were no significant between-group differences.

Why can mobile applications reduce alcohol use in people with AUD? It has been suggested that working memory training mobile phone applications may have a therapeutic effect by improving working memory in patients with SUD (6). Working memory training (WMT) is a promising way to improve working memory. A systematic review article by Brooks et al. showed that repeated WMT reduces brain activation in the frontoparietal and striatal networks, reflecting increased neural circuitry efficiency via myelination and functional connectivity changes. WMT could be utilized as a promising, effective, and non-invasive intervention for working memory deficits to treat impulse and affective control problems in people with SUDs.

AUTHOR CONTRIBUTIONS

KZ contributed to the writing of the Editorial.

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ORIGINAL RESEARCH
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Low-Theta Electroencephalography Coherence Predicts Cigarette Craving in Nicotine Addiction

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Addicts are often vulnerable to drug use in the presence of drug cues, which elicit significant drug cue reactivity. Mounting neuroimaging evidence suggests an association between functional magnetic resonance imaging connectivity networks and smoking cue reactivity; however, there is still little understanding of the electroencephalography (EEG) coherence basis of smoking cue reactivity. We therefore designed two independent experiments wherein nicotine-dependent smokers performed a smoking cue reactivity task during EEG recording. Experiment I showed that a low-theta EEG coherence network occurring 400–600 ms after onset during long-range (mainly between frontal and parieto-occipital) scalp regions, which was involved in smoking cue reactivity. Moreover, the average coherence of this network was significantly correlated with participants' level of cigarette craving. In experiment II, we tested an independent group of smokers and demonstrated that the low-theta coherence network significantly predicted changes in individuals' cigarette craving. Thus, the low-theta EEG coherence in smokers' brains might be a biomarker of smoking cue reactivity and can predict addiction behavior.

Keywords: electroencephalography coherence, nicotine addiction, smoking cue reactivity, external validation, functional connectivity

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INTRODUCTION

Nicotine addiction is a psychiatric disorder that is one of the leading causes of avoidable morbidity and mortality globally (1). One common feature of nicotine addiction is smoking cue reactivity, which refers to how nicotine-dependent patients show significant physiological and subjective reactions to cigarette-related cues (2). According to addiction theory, smoking cue reactivity is a central characteristic of nicotine addiction (3), and emerging evidence suggests that it is a precipitating factor in many relapse episodes (4). The reverse may also be true: that is, brain reactivity to smoking cues might predict the ability to maintain nicotine abstinence (5). Many studies have since explored the brain basis of smoking cue reactivity, given the potential clinical benefit this knowledge would have for the treatment of nicotine addiction.

Functional magnetic resonance imaging (fMRI) studies have shown that smoking cue reactivity involves many brain regions, including the anterior cingulate cortex, the superior frontal gyrus, the posterior cingulate cortex, etc. This suggests that the brain connectivity network is an important

basis of smoking cue reactivity (4, 6, 7). However, the low temporal resolution of blood-oxygen-level-dependent (BOLD) fMRI provides limited understanding of the temporal process of smoking cue reactivity (8). Numerous electroencephalography (EEG) findings suggest that smoking cue reactivity might be a relatively fast cognitive process (taking milliseconds). These findings showed that smoking cue reactivity tends to occur 300 to 800 ms after cue onset (9, 10). Although previous EEG studies have shown that smoking cue reactivity is related to the P300 (11), the slow positive wave (12), and the alpha power (10), these studies at best reveal that event-related potentials (ERPs) or time-frequency power were related to smoking cue reactivity, which provides rather limited understanding of the brain networks involved.

EEG coherence, as a measure of the brain network, which involves calculating the linear relationship between two electrode signals based on their cross-spectrum and estimating the synchronization between neural populations at a high temporal resolution, is believed to reflect functional cortical connectivity at the centimeter scale (13). This coherence is regarded as a direct reflection of the operation of corticocortical fiber systems or as an indirect reflection of the interactions of various brain networks including other cortical or subcortical structures (14). Therefore, EEG coherence has advantages on high temporal resolution and measuring brain network between populations of neurons. Recently Li et al. (15) used resting EEG coherence measure to explore the mechanism of hypnotic aversion suggestions on reducing cigarette craving. However, the EEG coherence basis of smoking cue reactivity is still unknown. In addition, so far few studies used other EEG measures of connectivity in nicotine addiction.

We designed two independent experiments to explore the EEG coherence basis of smoking cue reactivity. In experiment I, we found that smoking cue reactivity was related to increased low-theta (3–5 Hz) coherence at 400–600 ms after stimulus onset in long-range (between frontal and parieto-occipital) scalp regions. Additionally, craving—a core symptom of addiction that is often accompanied by drug cue reactivity—for cigarettes was significantly correlated with the average coherence of the low-theta network. In experiment II, an external validation demonstrated that the average coherence of the low-theta network predicted individuals' cigarette craving.

METHODS

Experiment I

Participants

Through online advertisements, we recruited 25 right-handed, unmedicated male nicotine-dependent smokers (≥10 cigarettes/day, ≥2 smoking years, aged 18–30 years) who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria for nicotine addiction as the smoker group, as well as 22 right-handed, healthy male adults (aged 18–30 years) as the nonsmoker group. All were studying at the University of Science and Technology of China. Because of the very low prevalence (only 2.7%) of female smokers in China, we enrolled only male smokers in this study. All had normal or corrected-to-normal vision. All participants gave their written informed consent before the experiment began and received financial compensation for completing it. The research protocol was approved by the Human Ethics Committee of the University of Science and Technology of China.

Experimental Procedure

Both groups completed a classical smoking cue reactivity task during EEG recording. Before the task, all participants recorded their demographic information including age and education years and completed the Toronto Alexithymia Scale (TAS) and the Positive and Negative Affect Schedule (PANAS). Furthermore, in the smoker group, we assessed cigarette craving before and after the smoking cue reactivity task using the Tobacco Craving Questionnaire (TCQ). Using the TCQ, we evaluated the change (i.e., increase) in cigarette craving pre-task to post-task. Participants were required to be abstinent from smoking cigarette for 2 h before the experiment. To ensure smokers' 2 h abstinence before the experiment, an experimenter would tell the participants not to smoke by telephone. And these smokers were also required to self-report the time of last cigarette smoked after arriving at the lab.

In the smoking cue reactivity task [adopted from our previous study (15); **Figure 1**], three kinds of cues [smoking (130 pictures), neutral (130 pictures), and animal (40 pictures)] were randomly presented to the participants. They were instructed to press the space bar on a keyboard as soon as possible when the animal picture appeared on the screen, in order to get them to focus their attention on the task. All these pictures were taken from our previous study (16). Each picture was displayed for 1 s and a fixation was presented during interstimulus intervals, which randomly varied from 1 to 1.5 s. For every 100 pictures displayed (about 3.7 min), participants were

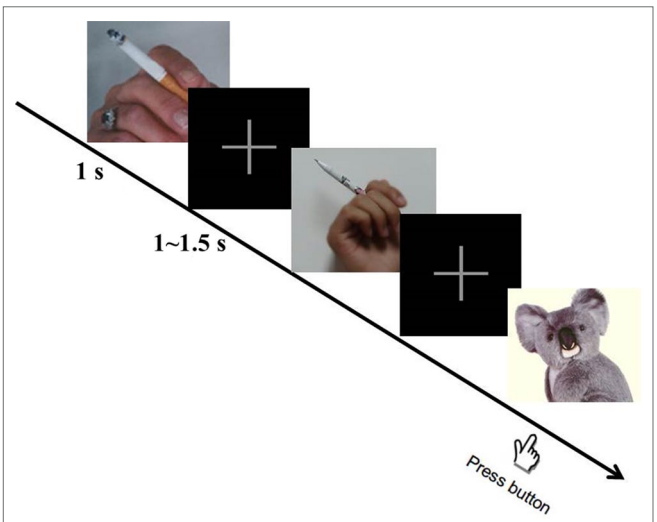

FIGURE 1 | Smoking cue reactivity task. During the task, participants were required to press the space button as soon as possible when the animal picture appeared. Three hundred pictures in total (including 130 smoking, 130 neutral, and 40 animal pictures) were displayed randomly. After participants viewed 100 pictures, they rested for 1 min.

asked to rest for 1 min. The smoking cue reactivity task lasted for about 15 min in total. All participants pressed the button correctly when the animal picture appeared (100% accuracy).

Electroencephalography Acquisition

The experiment task was run using the Psychophysics Toolbox for Matlab (http://psychtoolbox.org/). The EEG data were recorded using a SynAmps RT amplifier (NeuroScan, Charlotte, NC, U.S). Sixty-four Ag/AgCl electrodes were placed on participants' scalp at specific locations according to the extended International 10–20 System. Additionally, the electrical activities were recorded over the right and left mastoids. Vertical electrooculograms (EOGs) were recorded using bipolar channels placed above and below the left eye, and horizontal EOGs were recorded using bipolar channels placed lateral to the outer canthi of both eyes. The reference electrode was attached to the tip of each participant's nose and the ground electrode was attached to AFz. Impedance between the reference electrode and any recording electrode was kept under 5 kΩ. All the signals were digitized at 500 Hz during data collection.

Data Analysis

The raw EEG data during the smoking cue reactivity task were pre-processed, first *via* visual inspection to remove obvious technical artifacts, after which a high-pass filter was used to remove low-frequency noise and an independent component analysis was used to correct for blink artifacts. The continuous EEG data were then extracted into epochs from −200 ms (pre-stimulus) to 1,000 ms (post-stimulus) and baseline corrected using the interval from −200 to 0 ms. Epochs containing amplitude changes exceeding ±100 μv were rejected.

For the remaining epochs, spectral coherence, which reflects the connectivity between two electrodes, was calculated for every condition (e.g., smoking condition and the neutral condition) during the smoking cue reactivity task. To reduce the volume conduction effect, the electrode pairs for calculating spectral coherence were separated by at least 10 cm (14). Given that every trial lasted for about 1 s and the possible electromyography (EMG) artifacts for high frequency data, we calculated the spectral coherence from 3 to 30 Hz. To calculate the spectral coherence between two electrodes across epochs at each time-frequency region (TFR), the average cross-spectrum was calculated from the complex conjugate of the wavelet coefficients, after which it was squared and normalized using the average residual power spectrum of the individual electrodes. For each participant, the spectral coherence value between two electrodes at each TFR was calculated using the EEGLAB function *newcrossf*. For each TFR, the coherence matrix was constructed by calculating the coherence value between each electrode pair (>10 cm). The long range is that the interelectrode distances are greater than 10 cm. Previous studies have suggested that the short distances (<10 cm) may influence coherence measurements such that increased coherence can be measured even when the underlying sources are uncorrelated (14). Therefore, the long range (>10 cm) seems to reflect genuine group differences in coherent neuronal activity. To identify the significant TFR of the coherence network, we followed previous coherence analysis methods (14, 15): that is, the overall pattern of spectral coherence was computed by averaging all electrode pairs and then compared between the two experimental conditions across participants using nonparametric permutation test and false discovery rate (FDR) correction. Furthermore, the topography of the difference between the two conditions was plotted based on the significant TFR. The correlation between the average coherence within the network and the change in cigarette craving was measured using Pearson's correlation coefficient.

Experiment II

We recruited an independent group of nicotine-dependent patients (13 males; mean ± SD age, 26.8 ± 2.8 years; mean ± SD years of education, 15.9 ± 1.5 years) for experiment II. The EEG data during the smoking cue reactivity task were taken from another neurofeedback study of ours, obtained in the same manner as in experiment I. The participants of this study also completed several other cognitive tasks while the EEG was recording; however, these task data were used only in the other study. We used the EEG coherence network for smoking cue reactivity obtained in experiment I to define that in experiment II. Subsequently, the average coherence of the network was used to predict the change in cigarette craving through the same correlation model as in experiment I. The change in cigarette craving predicted by the EEG coherence network was then entered into a Pearson's correlation analysis with the observed change in cigarette craving. As in experiment I, we measured cigarette craving before and after the smoking cue reactivity task using the TCQ.

RESULTS

Experiment I

As shown in **Table 1**, there were no significant differences between the smoker and nonsmoker groups in age, education years, and TAS and PANAS scores, suggesting that both groups were homogenous in their characteristics.

To identify the significant TFR for coherence during smoking cue reactivity, we compared the overall patterns between the smoking and neutral conditions by averaging all electrode pairs. As shown in **Figure 2**, a significant low-theta TFR pattern (occurring 400–600 ms after stimulus onset in the 3–5 Hz band) was found in the smoker group. Furthermore, the low-theta TFR pattern was greater in the smoking condition than in the neutral condition. However, we found no significant TFR pattern differences between the smoking and neutral conditions in the nonsmoker group. Then

TABLE 1 | Baseline demographic characteristics of the two groups.

Characteristic	Smoker group	Nonsmoker group	*p*
Age (years)	26.4 (3.2)	26.8 (1.8)	0.65
Education (years)	15.7 (1.7)	15.3 (1.1)	0.41
Cigarettes/day	15.4 (5.7)	0	0
Years of cigarette use	6.3 (2.5)	0	0
TAS	66.8 (9.6)	63.5 (8.5)	0.25
PANAS			
Negative	24.5 (6.9)	24.6 (8.2)	0.96
Positive	32.6 (5.7)	31.7 (6.0)	0.66

Values are means (1 standard deviation). TAS, Toronto Alexithymia Scale; PANAS, Positive and Negative Affect Schedule.

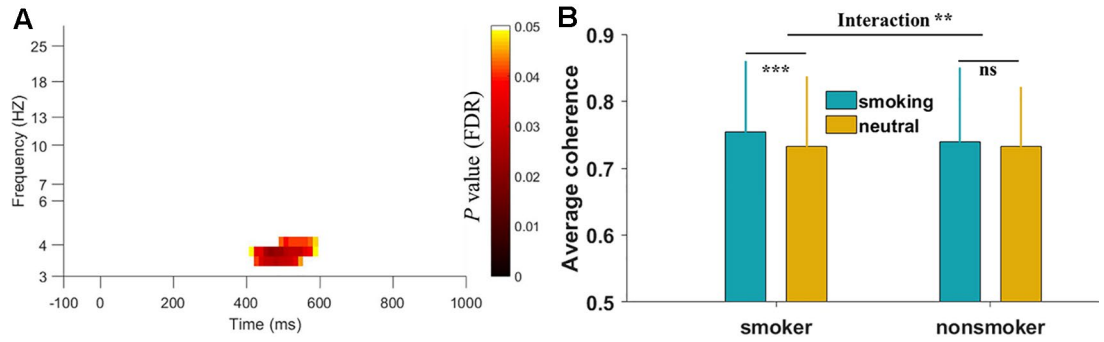

FIGURE 2 | Time-frequency region for overall electroencephalography (EEG) coherence in the smoker group and interaction results between two groups. **(A)** The significant region indicated that the overall EEG coherence in the smoking condition was greater than that in the neutral condition during the smoking cue reactivity task. The *p* values were corrected with the false discovery rate. Log transformation was applied on the y-axis frequency. **(B)** The interaction results on the average EEG coherence of selected time-frequency region between two groups. $^{**}p < 0.01$, $^{***}p < 0.001$, ns: not significant.

we performed a two-way mixed-design ANOVA analysis using group (smoking vs. nonsmoking people) as a between-subjects factor and cue type (smoking vs. neutral) as a within-subjects factor. We found there was a significant group-by-cue type interaction on the average EEG coherence [$F(1,45) = 7.23$, $p < 0.01$].

Figure 3 shows the topography of the condition differences in the significant low-theta TFR pattern. The smoking condition showed higher coherence for long-range (e.g., frontal and parieto-occipital) scalp regions than did the neutral condition among smokers, but not among nonsmokers.

As for the relationship between the low-theta network coherence and cigarette craving, **Figure 4A** shows a significant positive correlation between the average coherence of the low-theta network and the change in cigarette craving ($r = 0.41$, $p < 0.05$).

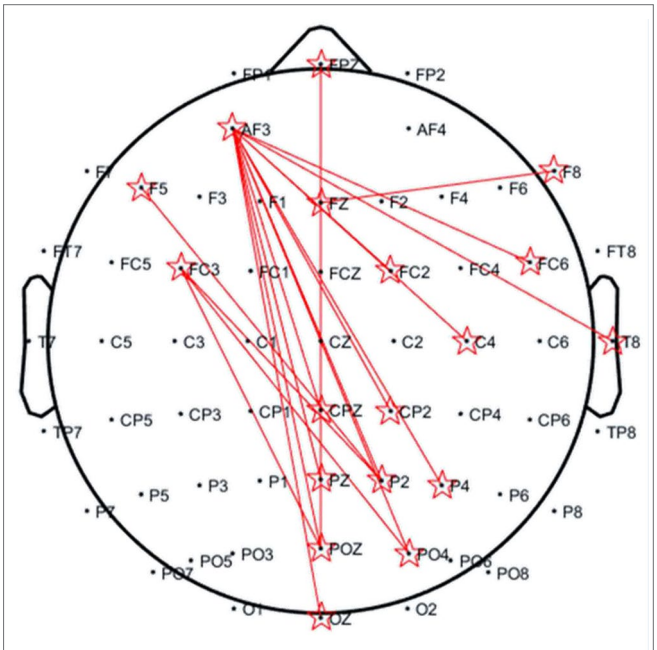

FIGURE 3 | Topography of significantly increased coherences in the 3–5 Hz band occurring at 400–600 ms for the smoker group. The distance of each electrode pair for calculating the coherence (reflected by red lines) was >10 cm.

Experiment II

In experiment II, the change in cigarette craving ranged from −23 to 14 (mean ± SD, 0.23 ± 9.98), which was similar to experiment I (mean ± SD, −2.72 ± 10.93; $t = -0.18$, $p = 0.42$). In this external validation, the estimated correlation model (y = 229.58*x-6.26) used to predict the change in cigarette craving was derived from the entire sample in experiment I. We found that the predicted change in cigarette craving using the low-theta network coherence was significantly correlated with participants' observed change in cigarette craving ($r = 0.70$, $p = 0.007$, **Figure 4B**); furthermore, they did not significantly differ ($t = -1.07$, $p = 0.30$). These external validation results indicate that the low-theta coherence basis of smoking cue reactivity significantly predicts the change in cigarette craving for a given participant based on the average coherence of the low-theta network.

DISCUSSION

In this study, we investigated the EEG coherence basis of smoking cue reactivity using the classical smoking cue reactivity task. First, we found increased coherence in the low-theta EEG network in the frontal-partial regions during smoking cue reactivity. Second, this low-theta coherence network was significantly associated with changes in cigarette craving. Finally, an external validation in an independent group of participants revealed that the average coherence of the low-theta network significantly predicted the change in cigarette craving.

In current study, nicotine-dependent individuals showed increased low-theta coherence during smoking cue reactivity when compared with nonsmokers. Our current findings build on these past studies by identifying some of the brain networks involved in smoking cue reactivity. Previous ERP and EEG oscillation studies revealed that smoking cue tend to elicit reactivity around the period between 300 and 800 ms after the cue appears (12), indicating

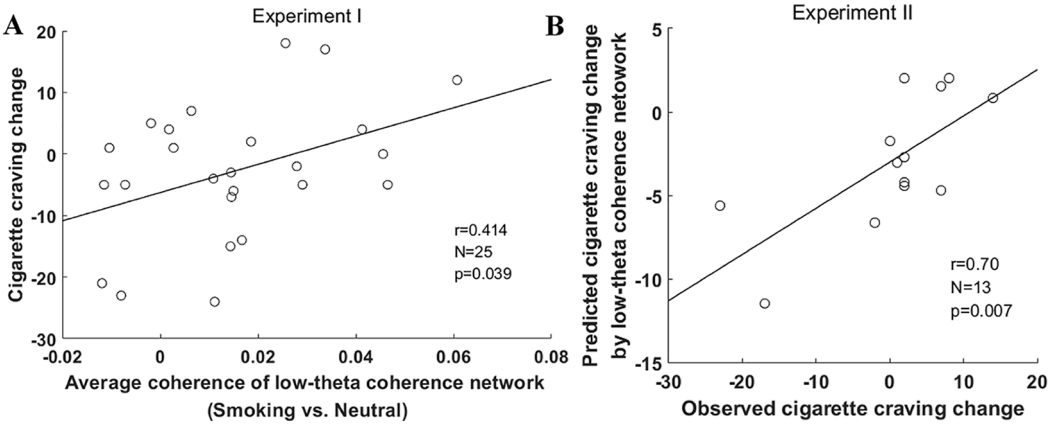

FIGURE 4 | Prediction of change in cigarette craving change by low-theta coherence network in the two experiments. **(A)** The correlation between cigarette craving change and the average coherence of the low-theta coherence network in experiment I. **(B)** The correlation between observed and predicted change in cigarette craving in experiment II. The change in cigarette craving indicated an increase from pre-task to post-task (post–pre).

that it is a relatively fast process. Our findings were well in line with the past studies, suggesting an early attentional deployment (arising between 400 and 600 ms reflected on low-theta band) on smoking cue. In addition, the frontal–parietal region connection (>10 cm) of the observed coherence network appears to be in line with the findings of a previous fMRI study showing that smoking cue reactivity was associated with the connectivity of the anterior cingulate cortices and precuneus (4). Moreover, the theta coherence from our second experiment has been shown to predict subjective craving level. Taken together, the current study may provide a novel and reliable biomarker for identifying smoking cue reactivity at both high temporal resolution and a certain degree of spatial resolution.

Smoking cue reactivity is accompanied by changes in cigarette craving (17). We found that the average coherence within the low-theta network was significantly correlated with changes in cigarette craving, thus supporting the idea the low-theta network is involved in nicotine addiction. Similarly, previous studies have shown that EEG theta coherence is associated with years of heroin use among people with heroin addiction (18). EEG theta coherence has also previously been found to be a biological marker of alcohol addiction (19). Collectively, these findings suggest the EEG theta coherence might play an important role in drug addiction.

Addiction studies have shown that cue reactivity involves numerous complex cognitive components (20), including attention, memory, emotion, etc. Long-range theta coherence has previously been found to be associated with working memory and sustained attention (21–23). Additionally, the scalp distribution of long-range theta coherence occurred primarily in regions where the memory and attention networks are localized (24). Based on these findings, we speculate that the low-theta coherence network we observed might represent memory and attention processes related to nicotine cue. However, to fully understand these mechanisms, concurrent EEG and fMRI experiments could be conducted to reveal precise network connectivity in future studies.

Recently, the replication of the results of neuroimaging studies has generated hot debate among researchers (25). Some studies are failing to be replicated, which might impede the healthy development of neuroimaging research as a whole (26). A potential reason for the lack of replication is that the generalizability of an internally validated prediction might be poor for a new sample (27). Therefore, we designed an independent experiment to externally validate the relationship between the low-theta coherence network and cigarette craving. The significant positive correlation observed between the observed change in cigarette craving and the predicted change based on the low-theta coherence network provide further evidence that this network might be a stable biomarker of nicotine addiction. This biomarker could therefore be an appropriate brain manipulation target for advanced neurofeedback or transcranial alternating current stimulation modulation technology for nicotine-dependent patients. However, these interventions require further investigation.

The present study is not without limitations. First, the sample size is not large, especially in the independent experiment. In addition, the participants' age is only from 18 to 30. Further studies should increase the number of nicotine-dependent patients and explore the EEG coherence mechanism of nicotine addiction in the different age group. Second, the spatial resolution of EEG coherence network was on a centimeter scale. Further studies could consider having the concurrent EEG-fMRI or magnetoencephalography (MEG) experiments to reveal complete brain basis of smoking cue reactivity.

To the best of our knowledge, this study is the first one to assess cortical connectivity during smoking reactivity through applying EEG coherence methods. The low-theta coherence we identified was a stable and novel biomarker for smoking cue reactivity that could be targeted for treating nicotine addiction.

ETHICS STATEMENT

The research protocol was approved by the Human Ethics Committee of the University of Science and Technology of China. All participants gave written informed consent prior to the study.

AUTHOR CONTRIBUTIONS

JJB and XCZ conceived and designed the study. JJB, RM, CF, SNS, YC, YP, and PYZ performed the research and analyzed the data. JJB, XCZ, RM, and CLL wrote the manuscript.

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BRIEF RESEARCH REPORT
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A Preliminary Examination of Nicotine-Free Electronic Cigarette Use During Cessation From Combustible Cigarettes

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Despite the availability of smoking cessation strategies, smoking cue-induced craving remains a relatively untreated relapse risk factor. Utilizing nicotine-free electronic cigarettes (e-cigarettes) to extinguish the motivational influence of smoking cues may be a viable approach to address cue reactivity. In this pilot study, 26 daily tobacco smokers used nicotine-free e-cigarettes while being maintained on daily transdermal sustained-release nicotine replacement therapy (NRT) to mitigate pharmacological withdrawal. Sensitivity to cue-induced craving, measured by the rise in craving after a visual cue exposure task, was assessed at a baseline visit after smoking as usual and again after 2 weeks of nicotine-free e-cigarette and NRT use. Participants' pattern and amount of tobacco cigarette smoking were evaluated on both visits and 1 month posttreatment. Cue-induced craving significantly decreased after the 2-week intervention, yet withdrawal scores increased during this time. One month after study completion, participants continued to report significantly lower overall cigarette craving and conventional tobacco cigarette use. Including the 34.8% that were totally abstinent, 65.2% reported smoking fewer than 10 cigarettes per week (compared to 87.2 per week at baseline for the entire group). A linear regression revealed that greater baseline cue-induced craving predicted better outcomes, whereas more withdrawal at the e-cigarette visit was related to more smoking at 1 month. This proof-of-concept pilot study suggests that the addition of *ad libitum* nicotine-free e-cigarettes to an existing strategy of transdermal NRT may attenuate cue-induced craving for tobacco smoking. A larger sample that is powered for detecting additional factors and longer-term outcomes is warranted.

Keywords: tobacco smoking, electronic cigarettes, nicotine replacement therapy, smoking cue reactivity, extinction

INTRODUCTION

Even when using available smoking cessation aids, relapse rates to smoking remain high (1). To address this limitation, there is the strong need to define treatments targeting relapse-precipitating factors, which are relatively unmitigated by standard pharmacotherapy. For instance, although symptoms of nicotine withdrawal can be attenuated by nicotine replacement therapy (NRT) and other pharmacotherapies, such as varenicline [for review, see Ref. (2)], smoking cue-induced craving is particularly difficult to mitigate, causing relapse months to years after cessation (3, 4). Although evidence strongly indicates that transdermal NRT does not attenuate cue reactivity (3–5), other studies suggest that medications, such as varenicline (6), and shorter-acting NRT, such as nicotine gum/lozenge (7), blunt cue reactivity. However, such medications are not consistently effective at reducing cue reactivity (8), and enhanced cue reactivity predicts relapse even when combined transdermal and short-acting NRT are used (9).

Collectively, this suggests the need for additional methods aimed at reducing cue reactivity, which potentially could be used in conjunction with currently available pharmacotherapy. Extinction is one potential behavioral method, where smoking cues are decoupled from acute nicotine administration, resulting in the devaluation of the smoking cues' motivational influence. Extinction therapies, such as cue exposure therapy (10), have been historically ineffective (11) partly because of context-driven renewal (12). Such renewal occurs when extinction takes place in a laboratory or clinical setting and does not effectively translate to real-world settings, leading to a "renewal" of cue reactivity in these contexts. Thus, there is the need to extinguish cues across real-life environments where individuals regularly smoke and encounter smoking-related stimuli.

It is plausible that cue reactivity may be reduced by replacing daily use of conventional tobacco cigarettes with non-nicotine-containing e-cigarettes when use occurs in environments where individuals typically smoke. In the short term, nicotine-free e-cigarette use may prevent relapse to smoking tobacco cigarettes by allowing the individual to continue to engage in behavior similar to smoking, without the reinforcing effects of nicotine, leading to a devaluation of smoking cues after repeated use. A limitation of using nicotine-free e-cigarettes alone is that individuals may still experience withdrawal symptoms. Adjunctive use of transdermal NRT may mitigate this issue because transdermal NRT provides a steady dose of nicotine to avert withdrawal symptoms without the reinforcing effects of dopamine bursts typically observed when nicotine is inhaled (13). The combination of non-nicotine e-cigarettes with transdermal NRT ensures that nicotine withdrawal and cue reactivity are simultaneously addressed. Although no other study to date has evaluated this combined approach, we designed the present proof-of-concept pilot study to test our theory that combining nicotine-free e-cigarettes with transdermal NRT is a viable strategy to allow individuals to engage in cue extinction without experiencing symptoms of acute withdrawal. Overall, this pilot study is the first step in assessing the potential utility of this combined treatment approach as a cessation tool that is specifically targeting cue reactivity.

METHODS

Participants

Twenty-six participants (eight females) who expressed a desire to quit smoking tobacco cigarettes were recruited between January 2015 and July 2018. Participants had to be between 18 and 45 years old, report smoking traditional cigarettes daily for at least the past 6 months, and be nicotine dependent, as measured by the Fagerstrom test for nicotine dependence (FTND) (14). Average participant characteristics are found in **Table 1**. Participants also had to express a willingness to transition from their regular cigarette use to the provided transdermal NRT and nicotine-free e-cigarettes. However, participants could not be currently using NRT or e-cigarettes and could only report infrequent use (<1× per month) of other forms of nicotine (cigar, pipe, chewing tobacco, etc.).

Participants were excluded for current illicit drug or alcohol dependence, major depressive disorder within the past 6 months, and current or lifetime history of schizophrenia, schizoaffective disorder, bipolar disorder, or psychotic disorders not otherwise specified [confirmed *via* Structured Clinical Interview for DSM-IV Axsis I disorders: Text Revision (SCID-IV-TR)]. Exclusionary criteria also included current serious medical illness, pregnancy, and recent drug/alcohol use (confirmed by the QuickTox11 Panel Drug Test Card, Branan Medical Corporation, Irvine, California; Alco-Sensor IV, Intoximeters Inc., St. Louis, MO). All procedures were completed at McLean Hospital, and the protocol was approved by the Partners Human Research Committee. Participants provided both verbal and written informed consent after receiving a complete description of the study.

Procedures

The overall study included four study visits: 1) **baseline visit**, where precessation metrics were collected, 2) A brief **check-in visit** 1 week after the baseline visit to assess compliance, 3) An **e-cigarette visit** 2 weeks after the baseline visit after the transition to transdermal NRT and nicotine-free e-cigarette use, and 4) a **follow-up visit** approximately 1 month after the e-cigarette visit to assess smoking behavior. The baseline and e-cigarette visits followed the same general timeline. The 2-week duration between

TABLE 1 | Represents participant characteristics as measured on the baseline visit. Data represent the mean and standard deviation (SD), except in the case of sex, which is noted as percent of total population and n.

	n = 26
Sex, % (n)	
Females	30.8 (8)
Males	69.2 (18)
Age	27.7 (5.7)
Years of education	15.1 (1.5)
Cigarettes per day	12.5 (6.1)
Expired CO	16.8 (12.1)
Pack-years	7.3 (7.0)
FTND scores	4.5 (1.8)
*Total Craving Score**	17.7 (6.7)

**Tiffany Questionnaire of Smoking Urges.*

the baseline and e-cigarette visits was chosen to allow for the transition to e-cigarettes. This duration also was chosen to prevent potential habituation to the cue reactivity task. Previous work has shown that cue exposure repeatedly evokes craving even with a shorter, 1-week duration between cue presentations (15).

Before the baseline study visit, participants were instructed to smoke as usual. Expired carbon monoxide (CO) was measured at the beginning of each study visit to provide a biochemical measure of smoking behavior. To standardize the duration between the last cigarette smoked and all procedures, participants smoked one of their own cigarettes (baseline visit) approximately 1 h before the cue exposure task. Craving was evaluated before and after cue exposure. After cue exposure, withdrawal was measured by the Wisconsin Smoking Withdrawal Scale [WSWS (16)] (~3.5 h after smoking).

At the end of the baseline visit, participants were provided transdermal NRT adjusted to their reported quantity of cigarette use (14 mg or 21 mg) and instructed in how to use this product. Participants also received nicotine-free e-cigarettes. The Apollo Challenger brand e-cigarettes (https://www.apolloecigs.com/en/e-cigarette-vape-kits/cigalikes-disposables/apollo-challenger-kit) were used, which are cigarette-like in appearance and were used in conjunction with the tobacco or menthol flavored e-liquid (matched to the participant's typical use) containing 0 mg nicotine. Participants were instructed to discontinue using their tobacco cigarettes at this time and were only to use the provided e-cigarettes, but they could use them as frequently as they liked. Participants were told that the amount of nicotine in both the e-cigarette and NRT combined was roughly equivalent to the amount they received in their typical smoking pattern, but that there was the possibility that the e-cigarette could contain no-nicotine. All participants received 0 mg e-cigarettes and were debriefed at the end of the study. To equate the study day timelines on the baseline and e-cigarette visits, participants used one of their e-cigarettes for 15 min approximately 1 h before the cue reactivity task. Between the baseline and e-cigarette visits, participants were asked to fill out daily diaries to document their use of e-cigarettes, NRT, and tobacco cigarette.

Measures

During the baseline and e-cigarette visits, subjective cigarette craving was measured using the Brief Questionnaire of Smoking Urges (QSU; 17) before (QSU_{pre}) and after (QSU_{post}) cue exposure. Change scores representing sensitivity to cue-induced craving were calculated by subtracting QSU_{pre} from QSU_{post}; thus, positive values represent enhanced cigarette craving after cue exposure. During the 1-month follow-up visit, the QSU was administered once without cue exposure. The QSU has a factor structure consisting of two factors: factor 1 is associated with reward and urge aspects of craving, whereas factor 2 is associated with mitigating symptoms of withdrawal (17). Both factors were considered in the subsequent analyses.

Cue Exposure Task

To measure sensitivity to cue-induced craving, participants completed a five-run, 26.5-min visual cue exposure task using the exact same protocol and validated images (visual cues) that we have used in our prior studies (18, 19). During this task, participants were shown 50 smoking, 50 neutral, and 10 target images in a pseudorandom order (only two images of the same type were shown in a row). This task was chosen because we have previously shown that it increases subjective craving after exposure to the cues (19). Participants were instructed to attend to all images and respond with a button press to the target images. Smoking images included smoking-related content, such as people smoking, people holding cigarettes, or cigarettes alone. Neutral images were matched for content in that they involved people, hands, or objects, such as pens or paintbrushes. Target images were animals, and participants were asked to press a button upon seeing a target image. This manipulation was included to ensure that participants attended to the task. Images were comparable but novel at each visit. A baseline manipulation check comparing craving (QSU factor 1) scores before and after cue exposure confirmed a rise in craving after task completion ($t(25) = -2.48$, $p = 0.020$).

RESULTS

Smoking Behavior

All 26 participants completed both the baseline and e-cigarette study visits. Daily diary self-report (N = 24; two participants did not complete this aspect) demonstrated that tobacco smoking was reduced on the first day that transdermal NRT and e-cigarettes were provided and remained below three cigarettes/day for the remainder of the 2-week period (**Figure 1**). Overall, participants used NRT on 66.5% of days and e-cigarettes on 87.3% of days while enrolled in the study, which was reflected by the rapid increase in their use on day 1 of the study after the baseline study visit. However, use of the NRT started to decline by the eighth to ninth day of the study and ended at 40% used on day 14. The reduction in daily tobacco cigarette use between the baseline ($M_1 = 12.46$) and e-cigarette visits [$M_2 = 0.16$; $t(23) = 9.95$, $p < 0.001$] was statistically significant (**Figure 2A**). This reduction in smoking was confirmed by significantly lower expired CO on the e-cigarette ($M_2 = 2.92$) visit relative to the baseline visit [$M_1 = 16.81$; $t(25) = 5.47$, $p < 0.001$; **Figure 2B**]. There was a significant rise in withdrawal measured by the WSWS from the baseline to e-cigarette visits [$M_1 = 42.8$; $M_2 = 49.4$, $t(25) = 2.3$, $p = 0.028$; data not shown]. No other form of nicotine use was reported during this period.

Changes in Cue-Induced Craving

On average, 15.32 ± 2.7 days separated the baseline and e-cigarette visits. A repeated-measures ANOVA of visit (baseline/e-cigarette), cue exposure (pre/post), and QSU factor (factor 1/factor 2) revealed that there was a significant three-way interaction [$F(1,24) = 11.56$, $p = 0.002$; **Figure 3**]. Significant interactions were also found between visit and factor [$F(1,24) = 26.63$, $p < 0.001$] and visit and cue exposure [$F(1,24) = 5.08$, $p = 0.03$]. A main effect of factor also was noted [$F(1,24) = 64.88$, $p < 0.001$]. Follow-up t-tests indicate that these findings were

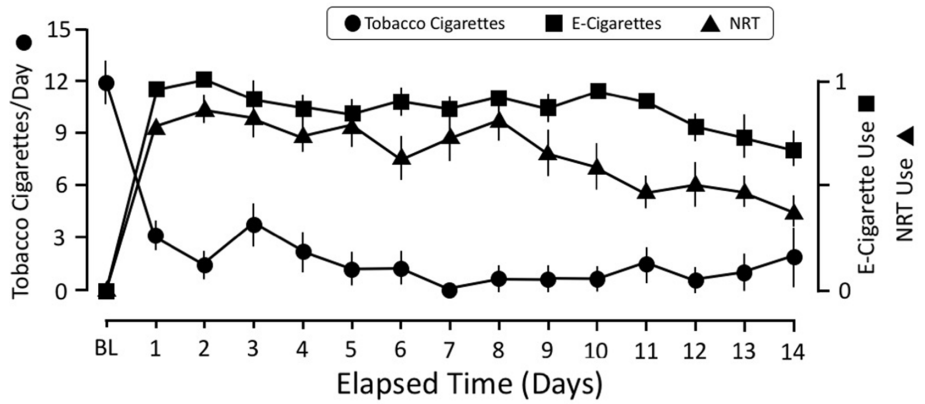

FIGURE 1 | Time course of smoking behavior, NRT, and e-cigarette use over the 2-week study. The scale for self-reported number of tobacco cigarettes is the average number of cigarettes per day. The scale for NRT and e-cigarettes was coded for either used or did not use that day. This strategy was adopted because it was difficult for participants to equate their e-cigarette use with number of "cigarettes." The e-cigarette data were coded as "1" if they reported using an e-cigarette that day and a "0" if they did not use it. The same strategy was used for tracking NRT use: a "1" indicated that they wore the patch that day, whereas a "0" indicated that they did not wear it. NRT, nicotine replacement therapy.

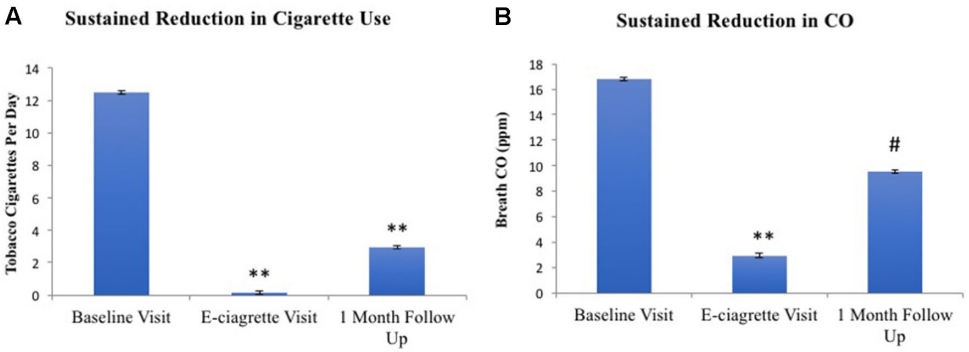

FIGURE 2 | Tobacco smoking **(A)** and CO **(B)** at all three study visits. Relative to the baseline visit, reduced levels of self-reported smoking and CO levels were noted on the e-cigarette and 1-month follow-up visits. $^{**}p < 0.001$, $^{\#}p = 0.053$.

driven by factor 1 of the QSU. Although factor 1 was significantly increased after cue exposure at baseline [$t(25) = 2.48$, $p = 0.02$], this rise was not observed during the e-cigarette visit [$t(24) = 1.36$, $p = 0.19$]. Factor 2 did not change after cue exposure on either visit. After cue exposure, factor 1 was greater during the baseline visit relative to the e-cigarette visit [$t(24) = 4.80$, $p < 0.001$], whereas no such effect was found for factor 2 [$t(24) = 0.15$, $p = 0.88$]. Finally, the elevation in craving after cue exposure (QSU_{post}-QSU_{pre}) was greater for factor 1 on the baseline relative to the e-cigarette visit [$t(24) = 2.86$, $p < 0.001$] but not for factor 2 [$t(24)$ 0.087, $p = 0.93$].

One-Month Follow-Up

One month after completing the study, 34.8% of participants remained completely abstinent from smoking tobacco cigarettes. An additional 39% of individuals were smoking less than three cigarettes per day. A paired samples t-test revealed that participants continued to report significantly lower tobacco cigarette use at 1 month ($M_2 = 2.94$) compared to baseline [$M_1 = 12.20$; $t(22) = 6.937$, $p < 0.001$; **Figure 4**], confirmed by an almost significant reduction in breath CO [$M_1 = 12.26$, $M_2 = 9.52$; $t(22) = 2.044$, $p = 0.053$; **Figure 4**]. Accordingly, cigarette craving (without cue exposure) was significantly reduced at the follow-up ($M_2 = 13.52$) as compared to baseline [before cue exposure; $M_1 = 17.83$; $t(22) = 3.963$, $p = 0.001$].

Predictors of 1-Month Cue Sensitivity and Cigarette Use

To determine whether cue-induced craving or withdrawal influenced the amount of tobacco smoking at 1-month follow-up, a linear regression was examined where number of cigarettes smoked per day was entered as the dependent variable. Baseline and e-cigarette values for WSWS and cue-induced QSU factor 1 differences ($QSU_{post\ cue\ exposure} - QSU_{pre\ cue\ exposure}$) were included as predictors. Overall, the model was significant $F(4,17) = 3.82$, $p = 0.022$ with an $R^2 = 0.47$ (**Figure 4**), which was driven, in part, by the baseline difference in QSU factor 1 (standardized = –0.39, $t = -2.13$, $p = 0.047$) and withdrawal as measured on the e-cigarette visit ($\beta = 0.630$, $t = 2.62$, $p = 0.018$).

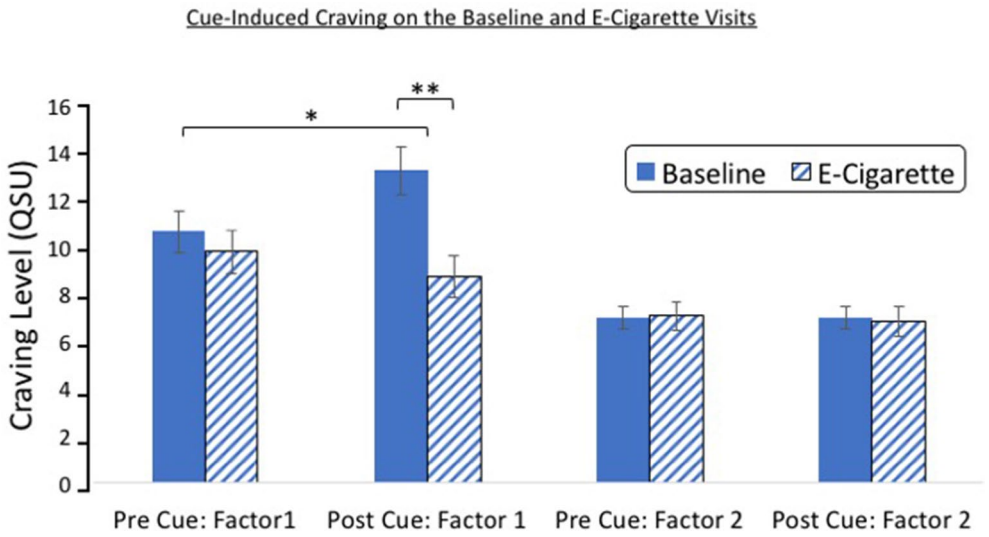

FIGURE 3 | Cue reactivity on the baseline and e-cigarette test day. A significant interaction was found between study visit (baseline/e-cigarette), cue exposure (pre/post), and QSU factor (factor 1/factor 2). Follow-up analysis indicated that this effect was driven by factor 1, which showed an increase after cue exposure on the baseline visit but not on the e-cigarette visit. Post-cue craving was greater on the baseline relative to the e-cigarette visit for factor 1. *p = 0.02, **p < 0.001. CO,carbon monoxide.

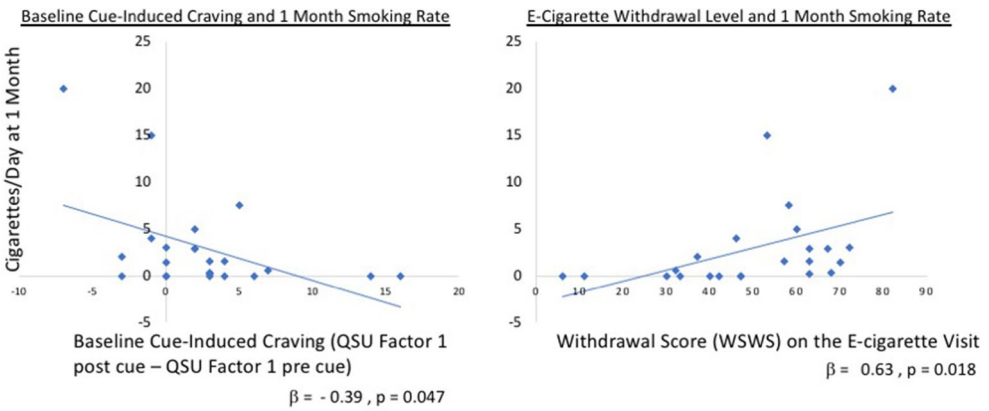

FIGURE 4 | Regression tobacco cigarettes/day versus QSU factors. Relationship between cigarettes smoked at 1 month and cue-induced craving at baseline (left panel; Factor 1 $QSU_{post\ cue}$ – Factor 1 $QSU_{pre\ cue}$) and withdrawal on the e-cigarette visit (right panel). Overall, the model including cue-induced craving and WSWS at both the baseline and e-cigarette visits was significant $F(4,17) = 3.82$, $p = 0.022$ with an $R^2 = 0.47$. This was driven, in part, by the baseline difference in QSU factor 1 (standardized β = –0.39, $t = -2.13$, $p = 0.047$) and withdrawal on the e-cigarette visit (β = 0.630, $t = 2.62$, $p = 0.018$). QSU, Questionnaire of Smoking Urges, WSWS, Wisconsin Smoking Withdrawal Scale.

DISCUSSION

The present pilot study provides initial evidence that smoking cue reactivity is reduced when nicotine-free e-cigarettes are used in conjunction with transdermal NRT. Consistent with our prior study (19), our cue reactivity task induced significant amounts of craving at the baseline visit. In contrast, enhanced cue reactivity was not present after 2 weeks of nicotine-free e-cigarette and transdermal NRT use. These findings were specific to QSU factor 1, which supports the notion that the motivational aspects of the cues were devalued. In contrast, there was no change in QSU factor 2 measures, which was unaffected by cues and focuses on the motivation to mitigate withdrawal-related symptoms. This reduction in cue-induced craving is unlikely to be caused by NRT because there is ample evidence demonstrating that transdermal NRT does *not* mitigate cue-induced craving at the doses examined here and at higher doses (3, 5). This implies that, for some individuals who are less impacted by withdrawal symptoms, the use of nicotine-free e-cigarettes alone may be sufficient to aid in abstinence. However, for this initial investigation, we chose to address both cue reactivity and pharmacological withdrawal to reduce the potential for relapse caused by either factor. This design is limited in that the effect of NRT and e-cigarettes alone cannot be separated, and the independent effects of each intervention require further testing.

It is unlikely that habituation played a role because cue reactivity elicits a consistent response even across multiple visits (6, 14). It should be noted that craving before cue exposure was measured after smoking either a tobacco cigarette during the baseline visit or an e-cigarette during the second visit. The fact that the magnitude of craving did not differ after smoking either type of cigarette suggests that recent smoking has a similar impact on craving in this context, regardless of cigarette type or nicotine content.

One interesting discovery was that individuals who had the greatest baseline reactivity to smoking cues appeared to benefit the most from this combined intervention. Our prior work showed that, when using NRT alone, highly cue-reactive individuals were more likely to relapse (9), indicating that the addition of nicotine-free e-cigarettes likely aided cessation in this otherwise vulnerable population. However, withdrawal symptoms were significantly elevated during the e-cigarette visit relative to the baseline visit, and such withdrawal symptoms after the intervention were associated with more smoking at the 1-month follow-up visit. This suggests that a longer, more traditional course of NRT or an alternative pharmacotherapy may be more effective when paired with non-nicotine e-cigarettes. Future experiments should evaluate cessation aids, such as varenicline, and combined transdermal and short-acting NRT (e.g., lozenges, gum). It is plausible that such pharmacotherapies and nicotine-free e-cigarettes may impact cue reactivity via different mechanisms and thus in combination may enhance efficacy. These types of approaches are needed to confirm this hypothesis.

This pilot study supports the proposed proof of concept that non-nicotine-containing e-cigarettes and transdermal NRT reduce cue reactivity. For reasons previously discussed, this initial work focused only on those receiving both treatments, and next steps will aid in documenting the influence of both interventions. Another limitation of the current approach is that the e-cigarettes used cannot be quantified into distinct units, such as "whole cigarettes," given that they do not burn down like combustible cigarettes. A single e-cigarette cartridge is equivalent to approximately one pack of cigarettes, but the length of time the cartridge lasts depends on how the individual uses it. For instance, one participant reported using the e-cigarette "continuously," making it difficult to equate to a specific number of individual cigarettes. Should products be developed that allow for more fine-grained assessment of e-cigarette usage, this would aid in the understanding of how much use is needed to see the currently reported reduction in cue-induced craving. However, the present work shows that 2 weeks of *ad lib* use results in reduced cue reactivity, suggesting that allowing individuals to titrate use based on personal desire is effective. Furthermore, although NRT and e-cigarettes were not provided to participants after the 2-week intervention, it is possible that participants independently sought out and used these products in the interim leading up to the 1-month follow-up visit. However, on the 1-month visit, participants did not report using either NRT or e-cigarettes. Extended use of both NRT and e-cigarettes likely facilitates abstinence, and larger clinical trials are needed to determine how long of an intervention is needed to sustain longer-term abstinence. The current preliminary findings support the potential of such an approach.

These results are promising and suggest that providing patients with nicotine-free e-cigarettes along with NRT should continue to be explored as a combination strategy to reduce cue-induced craving and relapse vulnerability. Although safety trials involving nicotine-free e-cigarettes have not been conducted, clinical trials studying nicotine containing e-cigarettes have reported low adverse events related to their use (20, 21). In the aggregate, it is possible that non-nicotine-containing e-cigarettes could be developed as a harm reduction and/or cessation strategy for tobacco smokers wishing to quit.

DATA AVAILABILITY

The datasets for this study will not be made publicly available because the work presented is preliminary and part of a larger on-going study and thus is still proprietary.

ETHICS STATEMENT

All procedures were completed at McLean Hospital and the protocol was approved by the Partners Human Research Committee. Participants provided both verbal and written informed consent after receiving a complete description of the study.

AUTHOR CONTRIBUTIONS

AJ and SL designed the experiment. AP, EM, and AJ conducted data analysis. MZ collected the data. AP created the initial manuscript draft, which was finalized by AJ and SL with the insight and feedback from all authors.

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Paliperidone Extended-Release Tablets for the Treatment of Methamphetamine Use Disorder in Chinese Patients After Acute Treatment: A Randomized, Double-Blind, Placebo-Controlled Exploratory Study

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Background: To test paliperidone extended-release (ER) for efficacy in decreasing methamphetamine (METH) use and reducing psychotic symptoms in METH-dependent patients after detoxification. Rates of adverse events with paliperidone ER versus placebo were also compared.

Methods: After discharge and 7 days without medication, 80 treatment-seeking METH-dependent participants were randomly assigned to paliperidone ER (3 mg once daily; n = 40) or placebo (once daily; n = 40) for 84 days under double-blind conditions. The participants attended clinics weekly to provide urine samples that were analyzed for METH metabolites, to complete research assessments, and to receive substance use and medication counseling.

Results: Fifty-six percent of follow-up visits and final visits were completed. The placebo group had a significantly lower retention [51.5 days; 95% confidence interval (CI), 41.6–61.4] than the paliperidone ER group (69.4 days,; 95% CI, 61.9–76.9; p = 0.016). Paliperidone ER was a protective factor against psychotic symptom relapse [hazard ratio (HR) = 0.15, p = 0.003]. Moreover, there were statistically significant effects of paliperidone ER on psychosis severity and METH craving, assessed by mean changes in Positive and Negative Syndrome Scale (PANSS) total scores, Clinical Global Impression—Severity (CGI-S) scores, and METH craving scores over time (p = 0.006, p = 0.002, and p = 0.03 for the medication-by-time interaction effect, respectively). There were no statistically significant differences between the two groups in METH use. There were no serious adverse events related to the study drug.

Conclusion: Compared with placebo, paliperidone ER administration resulted in a better retention rate and lower psychotic symptom relapse, but we did not find significantly reduced METH use among adults after acute METH detoxification treatment.

Keywords: methamphetamine, paliperidone extended-release, psychosis, exploratory study, efficacy, safety

INTRODUCTION

The use of methamphetamine (METH), an amphetamine-type stimulant (ATS), has increased to epidemic proportions worldwide, with an estimated 35 million people who used ATS drugs in 2015 (1). The number of registered ATS users also increased dramatically over the years in China from 0.36 million (27% of all registered drug users) in 2010 to 1.52 million (60.5% of all registered drug users) in 2016, and METH use is reported by approximately 78% of registered ATS users in China (2). METH use can contribute to psychosis, and the reported prevalence of psychosis, such as hallucinations and delusions, in METH users ranges between 10% and 60% and carries a high risk of concurrent violent behaviors (3, 5). Furthermore, over 50% of patients relapsed to METH use after treatment discharge (5, 6) due to the high potential for abuse and addiction to METH. This means that most patients had suffered the recurrence of psychosis resulting from METH relapse. In China, a large percentage of METH-dependent patients have suffered from the same situation in that they were repeatedly hospitalized due to METH-associated psychosis (MAP) (7).

METH administration causes a profound vesicular release of dopamine and serotonin and hypersensitivity to these receptors (8). While one randomized controlled trial had indicated that mirtazapine, an antidepressant, could significantly decrease METH use among active users, to date, no approved antipsychotic treatment has been found to be effective for the treatment of METH dependence. Risperidone's active metabolite, paliperidone (9-hydroxyrisperidone), is used for the treatment of schizophrenia and related disorders and acts as a dopamine (D2)/serotonin (5-HT2) receptor antagonist (9, 10). Several studies have indicated that paliperidone extended-release (ER) might have improved efficacy and safety compared with risperidone in the treatment of mental disorders (11) due to its different chemical characteristics, such as its affinity for D2 and α-adrenergic receptors and the pathway of its metabolism (12–15). To date, two open-label trials have shown that risperidone could reduce METH use (16, 17). One study indicated that risperidone blocks a high dose of METH-induced schizophrenia-like behavioral abnormalities (18), but no study has been conducted to investigate the efficacy and tolerability of paliperidone ER in the treatment of METH dependence and prevention of psychotic relapse after treatment discharge. We conducted a randomized, double-blind, placebo-controlled trial to test whether paliperidone ER would reduce METH use and psychotic relapse after treatment discharge.

MATERIALS AND METHODS

Study Overview

This trial was conducted between February 2013 and July 2015 in Wuhan Mental Health Center. The trial was sponsored and authorized by the Department of Psychiatry & Mental Health Institute of the Second Xiangya Hospital, Central South University. This study was carried out in accordance with the recommendations of the guidelines for clinical research from the Second Xiangya Hospital Ethics Committee, and all subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Second Xiangya Hospital Ethics Committee (NANDACRO (2012) CBNST-02).

Study Design

This was a double-blind, placebo-controlled, randomized exploratory trial in METH-dependent adults with MAP. Before the trial, we assumed that METH-positive urine samples would be decreased to 40% in the treatment group and to 60% in the placebo group based on data from published reports (19) and calculated that a sample size of 40 patients per treatment group would provide 96% power to detect an odds ratio of 3.5 in a design with 12 repeated measurements having a compound symmetry covariance structure. The correlation between observations on the same subject was 0.5, and the alpha level was 0.05 (20, 21).

Study Participants

The participants comprised recruits from voluntary drug treatment wards where detoxification with antipsychotic medication occurred and previous hospital inpatients who had been discharged. Men and women aged 18–60 years who met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, criteria for METH dependence with psychosis were enrolled in the study. The patients were included if they completed acute inpatient treatment (≤30 days) for METH use with remitted psychotic symptoms and 7 days without medication after discharge. Women of childbearing potential agreed to use contraception during the study. The exclusion criteria included pregnancy or breastfeeding; significant medical conditions (acute renal failure, endocarditis, active hepatitis, and tuberculosis); past or present history of an AIDS-indicator disease; aspartate amino transferase or alanine aminotransferase more than three times the upper limit of normal; known intolerance or hypersensitivity to paliperidone ER; other psychosis; and being dependent on substances other than METH or nicotine.

Study Medication

The paliperidone ER and placebo were in capsule form and identical in appearance and were prepacked in paper bags by others who were independent of the trial. After the research nurse obtained the patient's consent, she telephoned a contact who was independent of the recruitment process for allocation assignment. Each patient was assigned an order number and received capsules in the corresponding paper bags. One-week medication sealed packages were dispensed to the participants as the treatment allocation by a pharmacist with no involvement in the clinical or research activities of the study. Participants were instructed to take 3 mg daily for 1 week. The participants had to return all the packages, including the sealed and unsealed packages, during the next follow-up. The following additional medications were permitted: alprazolam (up to 0.8 mg/day) for agitation, anxiety, and insomnia (but not allowed in the morning prior

to scheduled assessments); lithium carbonate (1,000 mg/day); magnesium valproate (500 mg/day); benzhexol (2 mg twice daily) to attenuate the extrapyramidal symptoms induced by antipsychotics; and propranolol (10 mg thrice daily) to improve tachycardia (heart rate >100 per minute).

Randomization and Blinding

The study statistician with no involvement in the clinical or research activities of the study generated a 1:1 random allocation sequence using a fixed-block size of 8 and put the allocation sequence in sequentially numbered, opaque, sealed, and stapled envelopes. We separated the staff who made the assessment and the staff who delivered the intervention. The staff members who made the assessment were not informed of the treatment group assignment. Conversely, the intervention staff and psychologists did not make the assessments. All investigators, staff, and participants were kept masked to outcome measurements and trial results.

Procedures

The screening was performed by clinical staff when the patients completed inpatient METH detoxification and were discharged from the hospital. The screening included obtaining complete histories and physical information, blood counts, metabolic panels, liver function tests, and rapid qualitative urine METH tests using immunochromatographic METH metabolite detection. A reassessment was made on the seventh day after they left the hospital to exclude the patients who had relapsed to METH use, had a psychotic relapse, or used antipsychotic medications, followed by a baseline clinic visit during which randomization and drug dispensing occurred. The participants were seen weekly for psychotic symptom and METH craving assessment, urine collection, and physical exams for 12 weeks. The clinicians were psychiatrists and psychologists who were trained and received the National Certificate of Psychological Consultant and provided weekly 30 min cognitive behavioral therapy counseling sessions, during which the importance of taking the medication daily and how to handle missed doses were discussed. Safety assessments were performed at baseline and the final visit on day 84.

Outcomes

The outcomes included retention rates. Retention was defined as the duration of time spent in the trial for each individual and was calculated from the date a patient was randomized into the double-blind phase of the trial to the date the patient either completed or was officially withdrawn from the trial. The official withdrawal occurred when one or more of the following conditions were met: 1) the patient went without treatment for 7 days, 2) the patient was lost to follow-up for 2 weeks, and 3) the patient had to stop the trial for some reason. The recurrence of psychotic symptoms during the study, as determined by the time to the first experience of psychotic symptoms, i.e., a psychotic recurrence, was assessed through day 84. Psychotic symptom reoccurrence was defined as one or more of the following: 1) hospitalization for symptoms of psychosis (involuntary or voluntary admission); 2) deliberate self-injury or violent behavior or clinically significant suicidal or homicidal ideation; 3) 25% increase in the Positive and Negative Syndrome Scale (PANSS) total score for patients who scored >40 at randomization, or a 10-point increase for patients who scored ≤40 at randomization, for two consecutive assessments (i.e., within 1 week); and 4) increase in prespecified individual PANSS items scores (P1, P2, P3, P6, P7, and G8) to ≥5 for patients whose score was ≤3 at randomization, or to ≥6 for patients whose score was 4 at randomization for two consecutive assessments (i.e., within 1 week) (22). Changes in severity of psychosis, including change from baseline in weekly PANSS total score and Clinical Global Impression—Severity (CGI-S), were determined. Craving was assessed with a weekly self-report visual analog scale (VAS) of the need for METH (scale 0–10; 0 = not at all; 10 = very much so) (23). The confirmation of METH abstinence was assessed during the 12 weeks. Confirmed abstinence was defined as a negative urine drug test. The participants were seen weekly for urine collection. The following measures of urine drug test results were calculated: the longest period of METH abstinence during the 12-week study period and the treatment effectiveness score [TES; the sum of the number of METH-free urine samples submitted per participant (24)].

Safety assessments involved the recording of all adverse events (AEs) and severe AEs during the study. In addition, safety was assessed by monitoring hematology and blood biochemistry (including liver function tests, prolactin) and electrocardiographs at the baseline and end point.

Statistical Analyses

The efficacy analysis was performed on the intent-to-treat population. The differences in retention were evaluated using a Kaplan–Meier survival analysis. A Cox regression model was conducted to determine the association between the recurrence of psychotic symptoms and treatment group and to evaluate the hazard ratio (HR) of psychotic symptom recurrence in the paliperidone ER and placebo groups. All participants who did not have a psychotic recurrence, including those who withdrew or for whom the study was terminated without recurrence, were treated as censored observations, and time to censoring was calculated as the time from randomization to the last dose administered in the trial. The treatment was the main independent variable of interest, and sex, age category, and duration of METH abstinence were covariates in the analyses. We used the mixed-effect model repeated measure (MMRM) model to approach imputation of the data and analyzed the change from baseline in the weekly PANSS total scores, CGI-S, scores and VAS ratings. The t-tests were performed for the TES measure and the longest period of METH abstinence during the 84 days.

The safety population included all patients who received at least one dose of the study drug and was used in the analysis of all safety variables. For both populations, patients were analyzed according to treatment received. Differences in the incidence of AEs between the two treatment groups were evaluated using chi-square tests. Differences in the blood biochemistry tests,

hematology tests, and electrocardiographs from baseline to the end of treatment were evaluated by t-tests.

RESULTS

Screening and Randomization

The study period was from February 2014 to July 2016. The target sample size was achieved. **Figure 1** shows the results from the screening and the study arm assignment. Three hundred and thirty-six patients were assessed for eligibility, 105 of whom were ineligible. One hundred and fifty-one individuals were deemed eligible, and 80 agreed to participate and were randomized in the trial. Those who were eligible but did not participate in the trial were similar in age, race/ethnicity, and METH use status to those who were randomized.

The majority of study participants were men (71/80, 89%), the mean (SD) age of the group was 30.8 (7.0) years, and 49 of the 80 participants (61%) reported using METH 3–6 days per week prior to hospital admission. There were no significant differences in baseline characteristics or baseline clinical evaluation data between the two treatment groups ($p > 0.05$ for all comparisons). The baseline characteristics of the study participants are presented in **Table 1**.

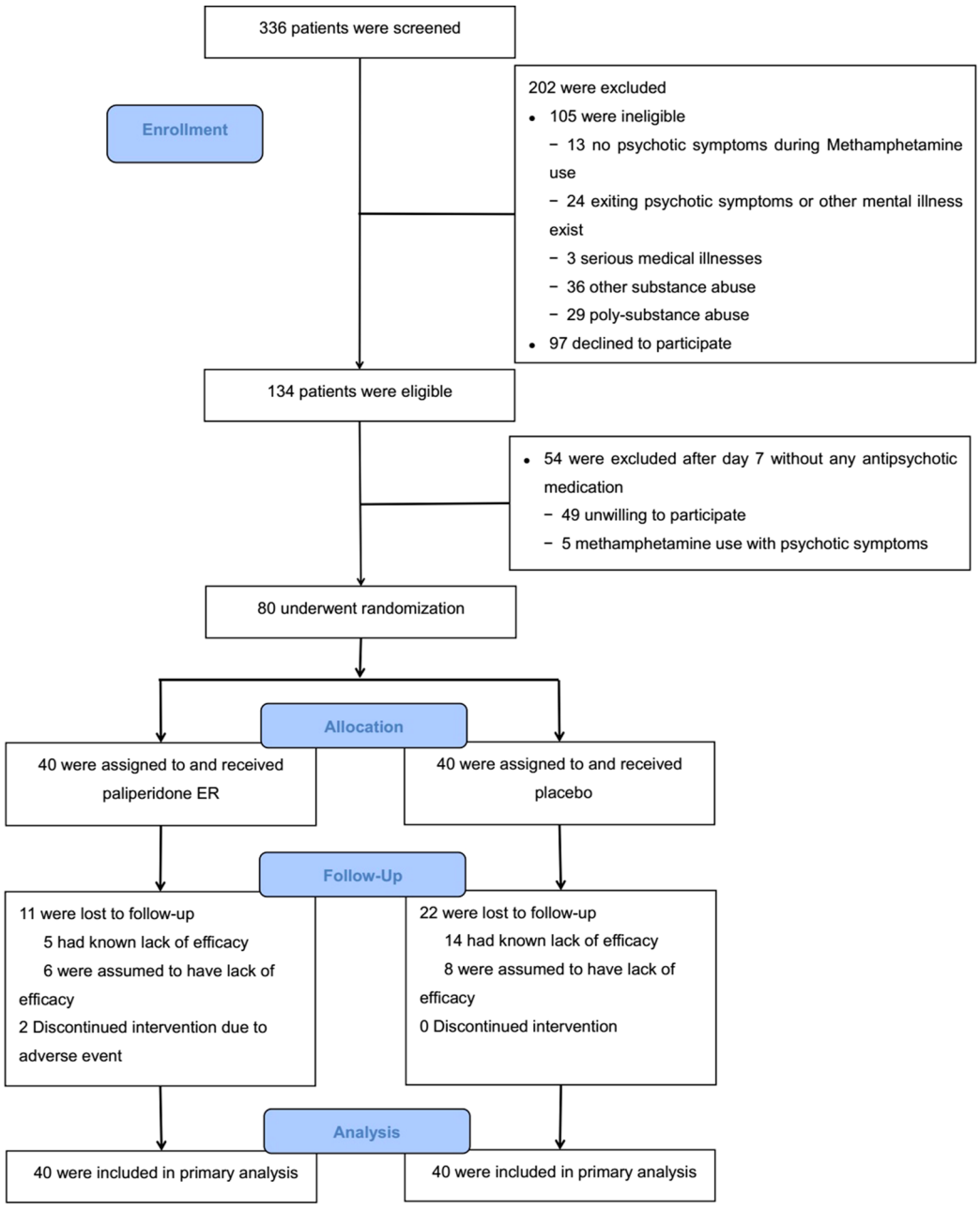


FIGURE 1 | Screening, randomization, and follow-up of study participants.

TABLE 1 | Baseline demographic and clinical characteristics of the sample (*N* = 80).

Demographics	Paliperidone ER	Placebo	Overall
	n = 40	n = 40	N = 80
Age, mean (SD), years	31.1 (7.0)	30.6 (7.1)	30.8 (7.0)
Sex, *n*			
Male	37	34	71
Female	3	6	9
METH use			
Onset age, mean (SD), years	26.9 (6.8)	26.0 (7.7)	26.5 (7.2)
Duration used, mean (SD), years	4.0 (2.0)	4.2 (2.6)	4.1 (2.3)
Frequency of METH use in past 4 weeks, *n*			
≤2 days/week	7	3	10
3–6 days/week	26	23	49
7 days/week	7	14	21
Route of METH administration, *n*			
Smoked	40	40	80
Nicotine dependence, *n*	39	40	79
Alcohol abuse, *n*	4	4	8
Baseline clinical characteristics			
PANSS total score (SD)	37.8 (5.4)	36.2 (4.3)	37.0 (4.9)
CGI-S (SD)	2.4 (1)	2.0 (0.7)	2.2 (0.9)
METH craving score (SD)	4.0 (0.8)	4.4 (1.0)	4.3 (0.9)
Weight, kg (SD)	74.3 (13.0)	70.7 (11.8)	72.5 (12.5)

CGI-S, Clinical Global Impression—Severity; ER, extended-release; PANSS, Positive and Negative Syndrome Scale score; SD, standard deviation; METH, methamphetamine.

Efficacy

Recurrence of Psychotic Symptoms

Our results indicated that participants in the paliperidone ER group had a substantially lower risk of psychosis recurrence than the subjects in the placebo group (HR = 0.15, p = 0.003). Furthermore, we found that a long duration of METH abstinence was associated with a lower risk of psychosis recurrence (HR = 0.93, p < 0.001) (see **Table 2**).

TABLE 2 | The Cox model measured the hazard ratio and 95% confidence intervals of psychotic symptom relapse associated with treatment.

Variable	HR	95% CI	*p* value
Group	0.15	0.04–0.52	0.003
Duration of METH abstinence	0.93	0.91–0.96	<0.001

Group includes paliperidone ER and placebo; HR, hazard ratio; CI, confidence.

Psychotic Symptom Severity and Methamphetamine Cravings

The paliperidone ER group maintained a relative improvement in psychotic symptom severity achieved: the mean PANSS total score and CGI-S scores remained stable. In comparison, the decreases in scores were significantly greater for patients in the placebo group (p = 0.006 and p = 0.001 for the medication-by-time interaction effect, respectively). Paliperidone ER treatment also resulted in a significantly greater improvement in the METH craving score than treatment with placebo. See **Table 3** for detailed results.

Treatment Retention and Medication Adherence

Overall, 56% of patients (45/80) completed the entire trial; however, the placebo group had a significantly lower retention [51.5 days; 95% confidence interval (CI), 41.6–61.4] than the paliperidone ER group (69.4 days; 95% CI, 61.9–76.9; p = 0.02), as shown in **Figure 2**. Psychotic recurrence resulting from relapse to METH use mainly led to discontinuation in the placebo group in contrast to the paliperidone ER group (13/40 or 32.5% in the placebo group vs. 4/40 or 10.0% in the paliperidone ER group; p < 0.05). The participants in the paliperidone ER group returned, on average, 63% of the 1-week medication sealed packages they had been dispensed compared to 56% in the placebo group (p = 0.06). Self-reported adherence was 76% in the paliperidone ER group and 68% in the placebo group (p = 0.07). Common reasons for nonadherence provided at the final visit included "simply forgot" (n = 56, 70%), "away from home" (n = 9, 11%), busy with other things (n = 27, 34%), "high on METH" (n = 18, 22%), and "did not want to take medication" (n = 15, 18%).

Urine Drug Screen Results

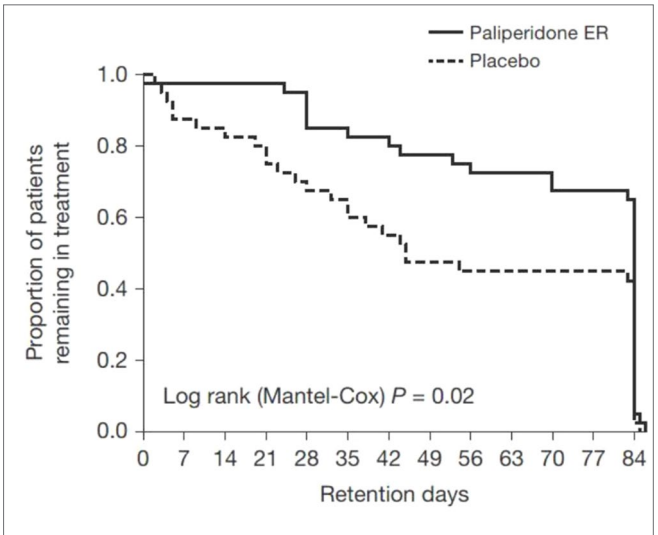
There were 705 urine drug tests obtained. During the whole trial, there were a total of 255 of 960 (26.6%) missing urine samples, including 76 (15.8%) of the total 480 in the paliperidone ER group and 179 (37.3%) of the total 480 in the placebo group; all missing samples were because of early termination.

There were no statistically significant differences in measures from the urine drug screen results between the two groups. Overall, 27.5% (n = 11) of the patients in the paliperidone ER group and 32.5% (n = 13) of those in the placebo group experienced a relapse to METH use. The mean TES and the longest period of METH abstinence during the 12 weeks were

TABLE 3 | Psychosis severity and METH craving results in both study groups.

	Baseline		Day 84		*p* value	
	Paliperidone ER (n = 40)	Placebo (n = 40)	Paliperidone ER (n = 27)	Placebo (n = 18)	Time	Group × Time
PANSS total score (mean, SD)	37.8 (5.4)	36.2 (4.3)	34.0 (3.9)	32.9 (1.9)	0.2	0.006
CGI-S (mean, SD)	2.4 (1)	2.0 (0.7)	1.6 (0.8)	1.6 (0.6)	0.3	0.001
METH craving score (mean, SD)	4.0 (0.8)	4.4 (1.0)	3.2 (0.9)	3.7 (0.7)	0.3	0.03

CGI-S, Clinical Global Imperssion-Severity; SD, Standard Deviation; ER, extended-release; PANSS, Positive and Nevative Syndrome Scale score; METH, methamphetamine.



ER = extended release.

FIGURE 2 | Proportion of patients remaining in treatment.

also not statistically significant between the two groups ($P = 0.14$ and 0.24, respectively). See **Table 4** for detailed results.

Safety and Tolerability

Paliperidone ER was generally well tolerated; only one patient in the paliperidone ER group discontinued owing to amenorrhea, which was deemed related to the study drug. The AEs reported in both treatment groups included akathisia (paliperidone ER: 6/40 or 15%; placebo: 2/40 or 5%; P = 0.1), insomnia (paliperidone ER: 17/40 or 42.5%; placebo: 21/40 or 52.5%; P = 0.3), and agitation (paliperidone ER: 18/40 or 45%; placebo: 23/40 or 57.5%; P = 0.3). Biochemistry and hematology tests and electrocardiographs showed no significant change from the baseline to end point in patients who completed the study. No overdose events, suicide attempts, deaths, or other severe AEs occurred.

At the study completion, participants were asked to guess their treatment assignment. There was no evidence of unblinding: 19/40 (48%) in the paliperidone ER group and 22/40 (55%) in the placebo group guessed correctly (p = 0.5).

DISCUSSION

This study demonstrated that paliperidone ER could reduce the risk of psychosis recurrence in METH users. Moreover, there was a significantly higher retention of patients in treatment among patients who received paliperidone ER. In the paliperidone ER treatment group, only 4 patients dropped out due to psychotic relapse after using METH, and most patients (7/11) returned for the scheduled evaluation visits, although they continued to use METH during the trial. In contrast to those in the paliperidone ER group, all the patients in the control group dropped out of the trial because of a psychotic relapse after using METH. These results suggested that paliperidone ER may have significant effects on psychotic symptoms among METH patients. Both the PANSS total scores and CGI-S scores decreased significantly in the paliperidone ER–treated subjects over time compared with the patients taking placebo, which further supported the findings that paliperidone ER improved psychosis severity in METH users. These results were consistent with two other studies (25). METH leads to excessive subcortical dopamine release and may induce behavioral sensitization, which is believed to be the central cause of MAP (8, 26). One study showed that risperidone could block a high dose of METH-induced schizophrenia-like behavioral abnormalities. Risperidone's active metabolite, paliperidone, mainly acts as a D2 receptor antagonist to possibly reduce the effects of high dopamine levels on the receptor and thus exert its effect on psychotic symptoms. As mentioned in the "Introduction," there is a high prevalence of psychosis in METH users and the potential development of disabling chronic psychotic illness (27). The escalating incidence of MAP presents a heavy burden on family and social and clinical services, and therefore, an early intervention is urgently needed. Many individuals experiencing such symptoms, however, do not seek help, and many clinicians do not pay enough attention to these presentations. Therefore, the reduction in the risk of psychotic recurrence in our study with paliperidone ER was significant for the treatment of METH use disorder.

An oral risperidone dose from 1 to 2 mg/day has been shown to be useful for lowering drug craving in patients with METH dependence (28), and another study using injectable risperidone showed the same result (17). In our study, patients did not show significant changes in METH cravings from the baseline to end point in either group. Despite their parent/metabolite relationship, paliperidone and risperidone have different pharmacological profiles. Paliperidone ER at a dose of 3 mg/day had a lower D2 receptor occupancy than an equivalent risperidone dose (2 mg/day) (12). This difference may contribute to the partially inconsistent results.

In our study, we did not find statistically significant differences between the paliperidone ER and placebo groups in METH use among these patients recently detoxified from METH, although METH use was lower in the paliperidone ER group over time. Our results are inconsistent with two previous studies that demonstrated the effectiveness of risperidone in treating METH dependence (16, 17), although there have been no studies that have reported on paliperidone ER treatment for METH dependence. The different findings may possibly be due to some of the following reasons. First, the study designs were not the same. Our study was a randomized, placebo-controlled trial, but the earlier studies were open-label trials, an uncontrolled design, making it difficult to reach firm conclusions about the efficacy of

TABLE 4 | Urine drug screen in both study groups ($N = 80$).

	Paliperidone ER (n = 40)	Placebo (n = 40)	*p* value
TES, mean (95% CI)	10.3 (9.2–11.4)	9.0 (7.4–10.5)	0.14
Longest METH abstinence (95% CI), days	10.3 (9.3–11.3)	9.3 (7.9–10.6)	0.24

CI, confidence interval; ER, extended-release; TES, Treatment Effectiveness Score; METH, methamphetamine.

risperidone in their population. We included subjects with MAP history but without current psychotic symptoms and METH use after detoxification, whereas in the previous two studies, subjects had psychotic symptoms and METH use, which may have resulted in the different average assessment data at the baseline between our study and the other studies. Therefore, our participants were more likely to represent the type of patients seen in real clinical settings in China, as mentioned above. In addition, different dosages of medication could also result in different outcomes. In our study, patients took paliperidone ER at a fixed dose of 3 mg/day [equivalent to risperidone 2 mg/day (29)], which was lower than the flexible dose range of 1 to 4 mg/day of oral risperidone or the fixed dose of 25 mg of injectable risperidone every 2 weeks used in earlier studies (16, 17). The higher doses of risperidone may be more effective for METH dependence.

In general, paliperidone ER 3 mg/day has been shown to be likely to cause AEs, such as headache, insomnia, anxiety, and sinus tachycardia, in the treatment of mental disorders. In our study, paliperidone ER appeared to be safe and well tolerated. There were no medication-related serious AEs except for one female patient in the paliperidone ER treatment who suffered amenorrhea, but the AEs attenuated after she discontinued taking paliperidone ER. The most frequently reported side effects/AEs were insomnia and agitation, and there were no significant differences in the number/frequency of such side effects between the two groups in our study. This indicated that these AEs may not be related to medication but to METH withdrawal symptoms.

This is the first study, to our knowledge, that studied the efficacy of paliperidone ER for METH dependence. Some of the limitations included a small sample size; therefore, we cannot rule out the benefits on METH use in the paliperidone ER group being as large as in the placebo group. Other limitations included the urban setting of our study location and the relatively lower retention and medication adherence relative to other studies (30, 19). Finally, our study did not assess cognitive functions, the efficacy of different paliperidone ER doses for METH use, or the relationship with patterns of METH use, such as frequency and dose of METH use.

In summary, paliperidone ER may be able to reduce psychotic recurrence, which is significant for minimizing these negative effects after METH use. However, we did not find evidence for paliperidone ER reducing METH use in METH dependence compared to placebo. Further studies should consider injectable paliperidone to improve medication adherence among patients and investigate the effects of different dosages.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Second Xiangya Hospital ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GW is involved in manuscript preparation and evaluated the participants. LM made substantial contributions to study conception and performed overall experiments. XL was responsible for randomization. XY put the allocation sequence in sequentially numbered, opaque, sealed, and stapled envelopes. SZ recruited and screened the patients. YY conceived and designed the experiments. ZX conducted the data analysis. WH participated in the critical revision of the manuscript and had final responsibility for the decision to submit it for publication.

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The Autonomic Progress Bar Motivates Treatment Completion for Patients of Stimulant Use Disorder and Cannabis Use Disorder

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Background: The intrinsic motivation behind the "need to complete" is more influential than external incentives. We introduced a novel progress-bar tool to motivate the completion of programs designed to treat stimulant and cannabis use disorders. We further examined the effectiveness of the progress bar's scoring approach in forecasting consistently negative urine tests.

Methods: This study's participants included 568 patients with stimulant, amphetamine-type, and cannabis use disorders who were undergoing 12-month mandatory treatment programs at Taichung Veterans General Hospital in Taiwan. Patients were given scores of 1, -1, or 0 depending on whether they received negative, positive, or missing urinalysis reports, respectively. The autonomic progress bar generated weekly score totals. At the group level, $score_i$ donated scores from all patients for a given week (i denoted the week). $Score_i$ was standardized to adjusted $score_i$. We then conducted Autoregressive Integrated Moving Average (ARIMA) Model of time-series analyses for the adjusted $score_i$.

Results: A total of 312 patients maintained treatment progress over the 12-month program. The autonomic score calculator totaled the shared achievements of these patients. The coefficients of the lag variables for mean (p), lag variables for residual error term (q), and number of orders for ensuring stationary (d) were estimated at $p = 3$, $d = 4$, and $q = 7$ for the first half of the treatment program, and were estimated at $p = 2$, $d = 2$, and $q = 3$ for the second half. Both models were stationary and tested as fit for prediction ($p < 0.05$). Sharply raised adjusted scores were predicted during the high-demand treatment phase.

Discussion: This study's novel progress-bar tool effectively motivated treatment completion. It was also effective in forecasting continually negative urine tests. The tool's free open-source code makes it easy to implement among many substance-treatment services.

Keywords: mandatory treatment, progress bar, motivation, stimulant use disorder, time series analysis

INTRODUCTION

Artificial intelligence advancements have enabled unprecedented reforms in the domain of medicine. These advancements have recently expanded to the addiction treatment field. In this context, both computer and mobile-based applications have helped eradicate the care gap while removing treatment barriers. Such tools also provide cognitive behavioral training, automated newsletter reminders, and treatment motivation (1–6). Many mobile apps have successfully been used to augment alcohol abuse treatment (4), while computers have become major intervention and meeting tools among therapists who need to monitor patient progress in cases of depression and marijuana use disorders (7). Further, several studies have reported that patients with stimulant use disorders require the ability to monitor their treatment progress online; such an environment offers enhanced motivation (8–11).

Progress bars are used as percentage-completion indicators (8). They are widely used in several software contexts, including program downloading, online gaming, and data transmission. In this regard, studies have found that the "need to complete" provides motivation (9, 10). From the psychoanalytic perspective, addicts cast powerlessness to therapists, who then produce a sense of powerlessness to form projective identities. As such, progress itself is seen as a reward (11, 12). We believe that progress indicators create intrinsic motivation through the "need to complete" and that that such urgency is more influential than external incentives.

If compulsory treatment is synonymous with the unwillingness to receive treatment, then it is unsurprising that psychotherapy resistance is profoundly manifested by many patients. Although difficult at times, mandatory treatment is thus becoming more common, especially because it increases treatment adherence. Mandatory treatment requires patients to follow prescribed treatment plans that sometimes require attendance schedules and scheduled urinalyses. We believe that 12-month treatment programs can achieve greater success if used in conjunction with effective computer software designed to facilitate psychological operations through the "need to complete." This will stimulate intrinsic motivation, thus prompting patients to adhere more closely to prescribed treatment plans. This study was comprised of two parts. First, we implemented a novel progress-bar tool to motivate treatment completion among patients of a 12-month program. Second, we examined the effectiveness of the progress bar's scoring approach (see *Measurements*) in forecasting continually negative urine tests.

METHODS

Samples and Materials

This was a retrospective follow-up study. Participants included 568 patients who were diagnosed with stimulant use, amphetamine-type, and/or cannabis use disorders between January 2013 and December 2018. All patients were required to complete 12-month treatment program at the Taichung Veterans General Hospital in Taiwan. All patients in this study were subjected to mandatory treatment. For inclusion in this study, patients were required to be at least 20 years of age and diagnosed with stimulant use, amphetamine-type, and/or cannabis use disorders based on diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders 5th Edition, DSM-5. We excluded patients who had completed fewer than four outpatient department visits upon treatment engagement. This ensured an adequate observation period for the time-series data. We also excluded patients whose most recent visit was more than 26 weeks before the study period. This was because confounding factors may have increased since that time. We also considered that missed treatments periods exceeding 26 weeks may have been due to factors related to the judicial system (e.g., patients had been rearrested and were required to start treatment anew). Those patients throughout the 12-month treatment program were selected to calculate the individual score (**Figure 1**). This study was approved by the ethics review committee at Taichung Veterans General Hospital (IRB number: CF18105A).

Treatment Protocol

The substance treatment service at Taichung Veteran General Hospital was based on an adapted protocol-driven design. This ensured robust treatment boundaries from a psychological perspective. Patients were required to complete the treatment intervention according to an attendance schedule and were subjected to both urinalysis and group psychotherapy.

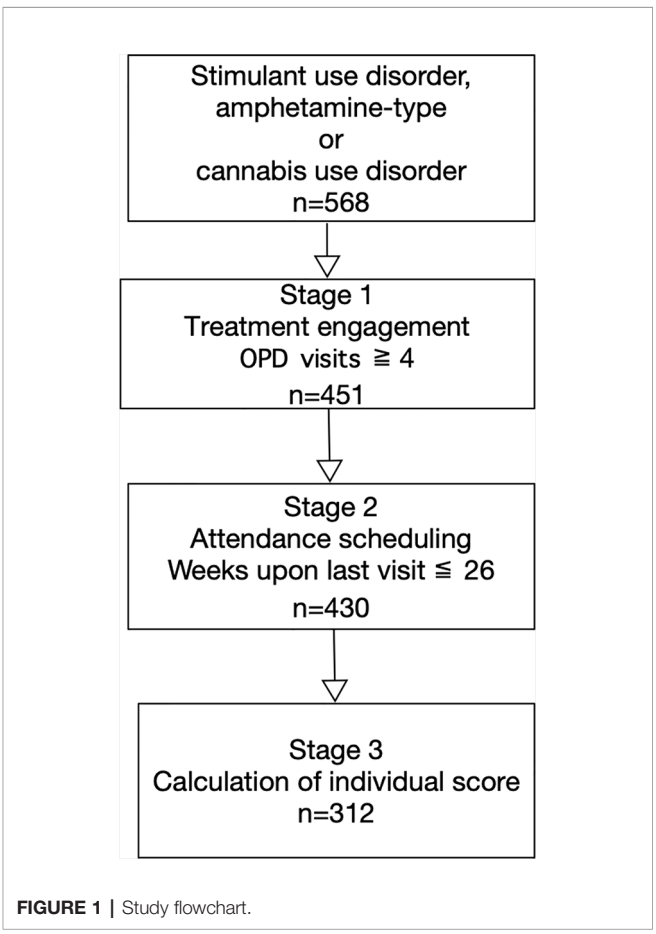

FIGURE 1 | Study flowchart.

Biweekly urinalyses were conducted to detect amphetamine, 3,4-Methylenedioxymethamphetamine (MDMA), and marijuana based on immunoassay during the first phase. For a given patient, stabilization was defined when a total of four negative urine samples had been observed. This was defined as the high-demand treatment phase.

Patients that completed the high-demand phase then transitioned to the low-demand phase. At that time, urinalysis was switched to a monthly basis. The average time at which patients began the low-demand phase was 6 months from treatment initiation. Here, each patient also attended a total of 10 biweekly group psychotherapy sessions. A positive urinalysis result required the respective patient to return to the biweekly urinalysis program.

Measurements

We developed a scoring system to summarize and visualize patient progress. Each patient received a score of 1 for each respective negative urinalysis result. However, each positive urinalysis resulted in a score of -1. Finally, patients received scores of 0 for each missed urinalysis. The program generated weekly score totals and plotted respective curves for each patient.

This scoring program consisted of a score and algorithm. At the group level, $score_i$ donated the total score from all patients in a given week (i denoted the week) (**Figure 2**). However, the number of patients who took urinalyses varied each week. As such, $score_i$ was standardized to the adjusted $score_i$. Adjusted $score_i$ was then calculated as $score_i/n$, where n denoted the number of patients who took urinalyses during $week_i$. The open-source code for the progress bar is offered for free in the **Supplementary Material** section at the end of this document.

Statistical Analysis

The adjusted $score_i$ for each week during the 12-month treatment period was used to generate time-series data. The milestone for reaching the low-demand treatment phase (see *Treatment Protocol*) was usually achieved approximately six months after beginning treatment. As such, two trend components were adapted at the 27th week as a cut-off point. We determined whether the time-series data deviated from the white noise assumption by implementing an Autoregressive Integrated Moving Average (ARIMA) Model, while an augmented Dickey-Fuller single root test was conducted to test stationarity. We also estimated the coefficients of the lag variables for mean (p), lag variables for residual error term (q), and number of orders for ensuring stationary (d). Finally, we used the Box-Pierce test to determine whether the model was sufficiently robust for prediction. The R software (version 3.4.4) package was used for all statistical analyses. Differences were considered significant at $p < 0.05$.

RESULTS

Of the 568 total patients, 117 failed treatment engagement as defined by attending less than four outpatient visits. Of the remaining 451, 430 maintained their expected attendance schedules. As such, 312 patients appeared consistently throughout the 12-month treatment program (**Figure 1**). Among these, 97.5% had stimulant use disorder, of which 37.0% used amphetamine-type stimulants more than 4 days per week. Of the abovementioned 312 patients, 79.1% were male (mean age of 36.0± 8.7 years), while 17.3% also had alcohol use disorder, and 10.1% had opioid use disorder. Overall, 8.0% were men sexed with men, and 7.8% were HIV-positive. Further, 10.6% had psychotic disorders, and 1.6% with bipolar disorder (**Table 1**).

For each patient, this study's progress bar generated a total weekly score through a user-friendly graphical interface. That is, the application functioned as an autonomic progress indicator. For example, a steadily rising curve followed by a sharp fall may have reflected relapse, while a steadily increasing accumulated score likely reflected abstinence throughout the treatment course (**Figure 3**).

$score_{i,j}$ ($_i$=1,2,..,52, $_j$=1,2,..,312)		$week_i$ ($_i$=1,2,..,52)				
		$week_1$	$week_2$	$week_3$	…	$week_{52}$
$patient_j$ ($_j$=1,2,..,312)	$patient_1$	$score_{1,1}$	$score_{2,1}$	$score_{3,1}$	…	$score_{52,1}$
	$patient_2$	$score_{1,2}$	$score_{2,2}$	$score_{3,2}$	…	$score_{52,2}$
	$patient_3$	$score_{1,3}$	$score_{2,3}$	$score_{3,3}$	…	$score_{52,3}$
	:				…	
	$Patient_{312}$	$score_{1,312}$	$score_{2,312}$	$score_{3,312}$	…	$score_{52,312}$
$Score_i$ ($_i$=1,2,..,52)		**$score_1$=** $\sum_{j=1}^{312} score_{1,j}$	**$score_2$=** $\sum_{j=1}^{312} score_{2,j}$	**$score_3$=** $\sum_{j=1}^{312} score_{3,j}$	**...**	**$Score_{52}$=** $\sum_{j=1}^{312} score_{52,j}$

FIGURE 2 | The definition of $score_i$ in this autonomic progress bar.

The progress bar facilitated patients in maintaining the vigilance needed to achieve their aims. In this context, we considered the addiction treatment service as an entity comprised of two halves. The first half was high-demand, while the second was low-demand. Patient progress during each half was measured according to $score_i$, which denoted the total scores from all patients in a given week (i denoted the week). **Figure 4** shows overall weekly patient performance throughout the 12-month program. Here, the crude scores reveal larger fluctuations during the initial stages.

Total scores were dependent on the number of patients who completed urinalysis. Because the treatment protocol followed a biweekly schedule, the number of patients doing so was higher during weeks 2, 4, 6, and 8 than during weeks 1, 3, 5, and 7 (**Figure 4**). Given that the number of patients who completed urinalysis varied each week, $score_i$ was standardized into adjusted $score_i$. After standardization, adjusted scores showed reduced interference due to varied attendance. On the other hand, we found increased fluctuations in the adjusted score during the second half of the treatment program.

The first half of treatment revealed a trend spanning from week one to week 26, while the a second trend component was observed between week 27 and week 52. The coefficients of the lag variables for mean (p), lag variables for residual error term (q), and number of orders for ensuring stationary (d) were estimated at $p = 3$, $d = 4$, and $q = 7$ for the first half of the program, but were estimated at $p = 2$, $d = 2$, and $q = 3$ for the second half. Both models were stationary and tested as sufficiently fit for prediction ($p < 0.05$). Using the above two ARIMA models, we predicted an adjusted score that would reflect treatment outcomes during each program phase. Here, a sharply raised adjusted score was predicted during the high-demand phase, thus indicating an increasing number of negative urine tests. However, a slow and steady raised adjusted score was predicted for the low-demand phase (**Figure 5**).

DISCUSSION

We introduced a novel autonomic progress-bar tool to summarize urinalysis results for patients who were attempting to complete a program to treat stimulant and/or cannabis use disorder. We also developed an autonomic score calculator that totaled shared patient achievements. Resulting scores were analyzed as time-series data, thus revealing a trend that reflected compatible treatment demands.

TABLE 1 | Descriptive data of 312 patients of stimulant use disorder or cannabis use disorder completing 12-month treatment.

Baseline	Mean ± SD	N(%)
Male		247(79.1)
Age	36.0±8.7	
Stimulant use disorder		305(97.5)
Amphetamine use ≧ 4 times/ week		115(37.0)
Alcohol use disorder		54(17.3)
Opioid use disorder		31(10.1)
Men sexed with men		25(8.0)
HIV positive		24(7.7)
Psychotic disorder		33(10.6)
Bipolar disorder		5(1.6)

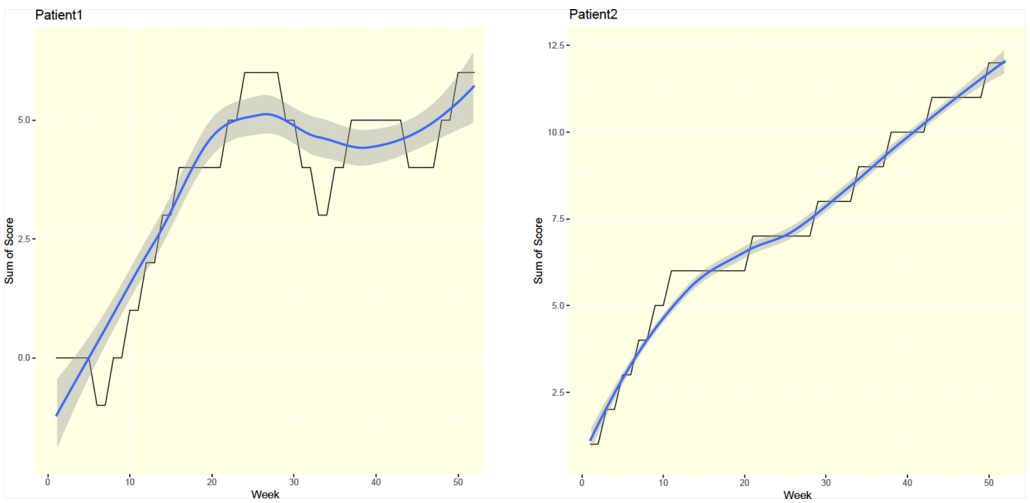

FIGURE 3 | Two examples of patient's progress bar.

This visual progress bar is currently a preliminary tool. However, elements of the intuitive design should be retained. For example, steadily increasing accumulated scores reflected persistent abstinence throughout the treatment course. Additional animated indicators may generate a curiosity-driven and pleasant experience. This is important because such factors are associated with the novelty-seeking trait (13, 14). We therefore believe that our progress bar will promote treatment engagement among patients with stimulant and/or cannabis use disorder.

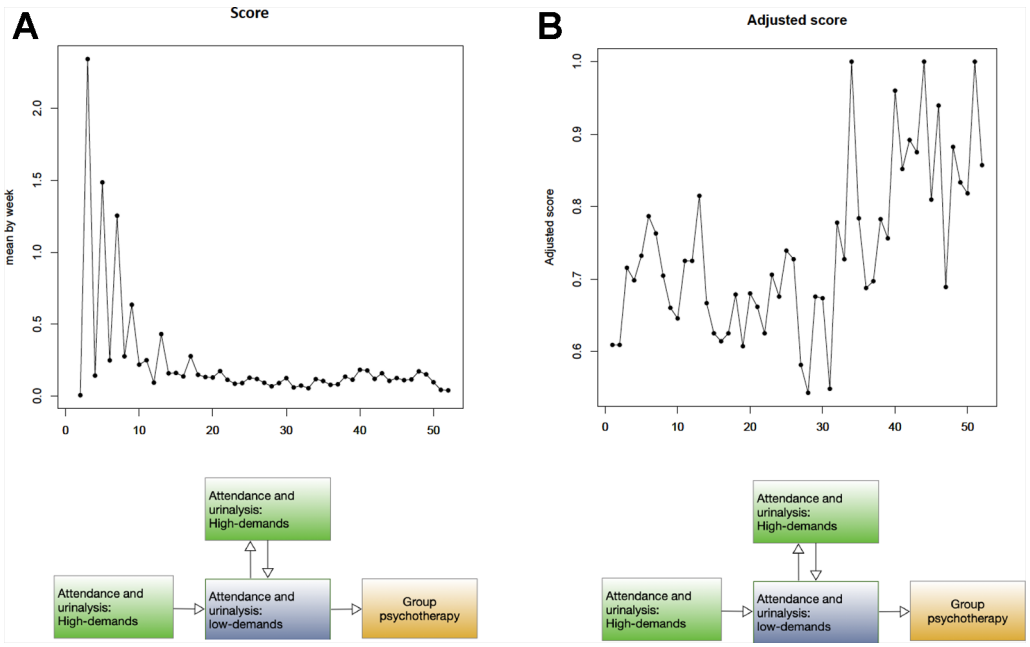

FIGURE 4 | Time-series plot of overall 312 patients **(A) X**-axis: week, **Y**-axis: score **(B) X**-axis: week, **Y**-axis: adjusted score.

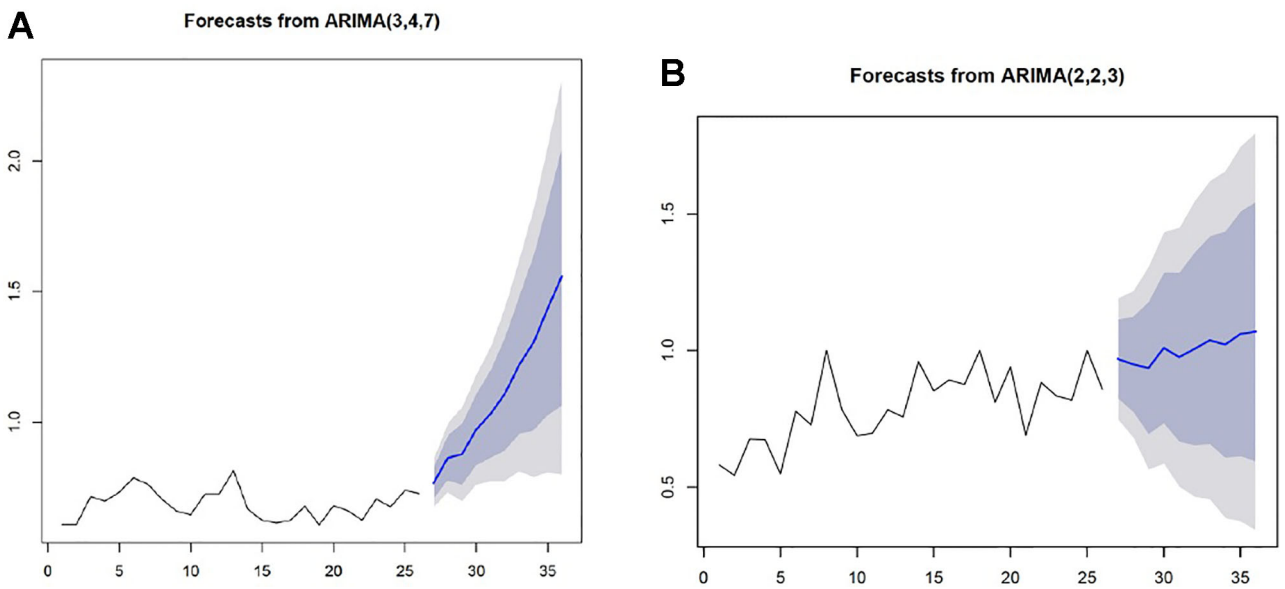

FIGURE 5 | The ARIMA models predicting treatment outcomes for each phase **X-axis**: week, **Y-axis**: adjusted score **(A)** A sharply raised adjusted score indicating an increased number of negative urine tests was predicted for the high-demand treatment phase. **(B)** A slow and steady raised adjusted score was predicted for the low- demand treatment phase.

Drug users may experience distress over the perception of lagging in progress. It is thus crucial to provide a virtual method for these individuals to generate forward-looking attitudes while preventing relapse (9, 15). Our visual progress bar offers a rewarding effect rarely obtained in contexts outside treatment programs. It may also offer experiences of increased mental engagement related to information-valuing functions, particularly those in the dopaminergic valuation systems (16, 18). From the perspective of neural encoding, information prediction during non-instrumental information seeking is not prone to error (16). This produces greater feelings of self-competence and promotes treatment adherence (19–20).

This study examined the effectiveness of a scoring approach through a visual progress bar in forecasting continually negative urine tests. We also examined performance at different treatment stages associated with changing demands and considered how the scoring system could be improved. As such, we plotted two ARIMA models to conduct time-series analyses for both the high and low treatment demand phases. We found obvious changes in scores based on treatment demands. For example, rapidly increasing scores reflected an increasing number of negative urine tests, which was forecast for the high-demand phase. On the other hand, a series of small, incremental score increases were predicted for the low-demand phase. Previous research has also shown that high-demand treatment is significantly correlated with continually negative urine testing (21). Here, the changes in scoring trends between the different treatment levels observed in this study supported existing evidence.

We found increased fluctuations in the adjusted score during the low-demand treatment phase. This is likely because the number of patients completing urine tests under the stringent biweekly schedule dwindled over time. For example, a given patient would complete urine testing during even-numbered weeks if following the attendance schedule exactly. However, missed appointments would disrupt the schedule, thus increasing the number of tests taken during odd weeks. As such, the numbers of patients attending during even and odd weeks were distributed more evenly over time. This was reflected by the fluctuating scores seen during the second half of the treatment program.

This study should be interpreted within the context of its limitations. First, we did not examine the validity of the progress bar through a clinical trial. This study did not compare a non-progress-bar-using group and a progress-bar-using group. Instead, we incorporated a quasi-experiment. As a result, the validity and reliability of this novel tool could not be determined. Second, patients were required to attend biweekly group psychotherapy sessions that began during their six months of treatment. As such, an instrumental effect due to this therapeutic influence may have been a confounding factor. Third, all patients in this study were subjected to mandatory treatment. This was because treatment approach for substance use offenders transited from detention-base to deferred prosecution, for recent two decades globally. Previous study proved the judicial-plus-therapeutic effect rather than judicial-alone effect (21).

In conclusion, we developed a novel progress-bar tool for use in motivating the completion of a stimulant and/or cannabis use treatment program. We also developed an autonomic score calculator that totaled shared patient achievements. Finally, a time-series analysis was conducted to examine the effectiveness of both the scoring approach and progress bar in forecasting continually negative urine tests. The open-source code for this free application is offered in the Supplementary Material section below and can easily be implemented for use in other substance-treatment services.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation, to any qualified researchers.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Committee of Taichung Veterans General Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

I-CC contributed to statistical analysis and drafting of the manuscript. GT contributed to the conception and interpretation of data. C-JC, T-HL and H-JL contributed to revising critically of the intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00944/full#supplementary-material

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Dissociable Effects of Theta-Burst Repeated Transcranial Magnetic Stimulation to the Inferior Frontal Gyrus on Inhibitory Control in Nicotine Addiction

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Nicotine addiction, like other substance use disorders (SUD's), is associated with deficits in prefrontal mediated inhibitory control. The strength of inhibitory control task-based functional connectivity (tbFC) between the right inferior frontal gyrus (r.IFG) and thalamus (corticothalamic circuit) mediates the association between successful inhibition and smoking relapse vulnerability. However, the potential efficacy of theta burst stimulation (TBS) to the r.IFG, a treatment known to alter clinical symptoms among neuropsychiatric patients, has not been reported in a SUD population. This study utilized fMRI guided neuronavigation to examine the effects of TBS on inhibitory control among nicotine dependent individuals. Participants (N=12) were scanned while performing an inhibitory control task known to elicit inhibition-related activity in the r.IFG. Using a randomized, counterbalanced cross-over design, participants then received TBS over two visits: excitatory (iTBS) on one visit and inhibitory (cTBS) TBS on the other visit. The effects of each TBS condition on subsequent inhibitory control task performance were examined. A significant condition x time interaction was identified on trials requiring inhibitory control ($F(1,10) = 7.27$, $p = .022$, $D = 1.63$). iTBS improved inhibitory control, whereas cTBS impaired inhibitory control. Brain stimulation did not influence performance in control conditions including novelty detection and response execution. This is the first study to demonstrate that non-invasive neural stimulation using iTBS to the r.IFG enhances baseline inhibitory control among individuals with a SUD. Further research is needed to directly examine the potential parametric effects of TBS on corticothalamic tbFC in individuals with a SUD.

Keywords: fMRI, TBS, TMS, tobacco, inhibition, executive, brain, cognition

INTRODUCTION

Substance use disorders (SUDs) are characterized by significant disruptions to multiple forms of executive function (1) and the extant literature implicates dysregulated inhibitory control, one specific form of executive function, as a transdiagnostic indicator of relapse vulnerability across substances of abuse (2). In the context of tobacco use disorder (nicotine addiction), smokers, as compared to non-smokers, exhibit significantly worse performance on tasks that probe inhibitory control (IC) (3–5); and among smokers, smoking abstinence as compared to satiety, further disrupts inhibitory control task performance (6, 7). Furthermore, baseline inhibitory control task performance is significantly associated with smoking outcomes following a quit attempt (8, 9) and the capacity to resist ad lib smoking in a laboratory setting (9, 10). Despite compelling evidence of IC deficits contributing to the maintenance of nicotine addiction, there is little support for the therapeutic value of existing first line FDA approved smoking cessation medications for treating inhibitory control mechanisms (11, 12). Therefore, there is a need for mechanistic research to identify new strategies for treating IC pathophysiology in tobacco use disorder.

The extant literature converges on a role of the right inferior frontal gyrus (r.IFG) as a key prefrontal region involved in the initiation of a "stop" command (13, 14). Individuals with a substance use disorder (2), including tobacco use disorder (15–17), exhibit greater fMRI BOLD response in the r.IFG during task probes of attention (18) and inhibitory control (6) that may represent a compensatory mechanism to meet task demands. Given strong evidence for the involvement of r.IFG in inhibitory control and smoking related dysregulation in r.IFG mediated inhibition, examining whether neural stimulation to the r.IFG can modulate inhibitory control in smokers represents an important avenue for examination.

Thetaburst stimulation, a form of patterned transcranial magnetic stimulation (tb-pTMS) can be used to modulate neuronal function within a focused area, as well as functionally connected brain regions. TBS has a good safety profile (19, 20) and is administered in two forms: a) Intermittent TBS (iTBS) (21) which enhances spontaneous neuronal firing (22) and induces long-term potentiation (LTP)—putatively strengthening neural activity (23); and b) Continuous TBS (*c*TBS) (24) which induces long-term depression—putatively dampening neural activity. The effects of LTD-like *c*TBS to r.IFG have been reported in two studies with healthy controls, demonstrating that *c*TBS disrupts inhibitory control task performance (25, 26), but not performance in other, task-related domains (general attention, generic responding) (25). However, to the best of our knowledge, there is no published work, either in a healthy or in a clinical sample, on the effects of iTBS—the pattern with potential therapeutic value—to r.IFG on inhibitory control.

Therefore, given the lack of known medications for treating inhibitory control deficits among smokers and the unknown potential of iTBS for modulating inhibitory control among individuals with an SUD, the goal of the current study was to examine the effects of TBS on inhibitory control task performance in smokers. To this end, r.IFG regions involved in inhibitory control were identified for each individual (N = 12) using fMRI data acquired during performance of a validated IC test. Using a crossover design, we examined the effect of both excitatory (iTBS) and inhibitory (cTBS) TBS to the r.IFG on inhibitory control task performance in each individual. We hypothesized that the excitatory stimulation would improve, and that the inhibitory would disrupt, IC task performance. The effects of TBS on novelty detection and generic motor responding were also assessed.

MATERIALS AND METHODS

Participants

Twelve healthy adult (age: M = 31.42 years ± 7.39, three females, education: M = 13.00 years ± 1.35) nicotine dependent (FTND: M = 5.42 ± 2.19) smokers, smoking on average 16.42 ± 4.52 cigarettes per day for 13.83 ± 7.57 years completed the study (see **Table 1**). Inclusion criteria were being in good health, right-handed, aged 18-55 years, and smoking ≥ 10 cigarettes/day. Exclusion criteria were having significant health problems, contraindications for MRI, use of psychoactive medications, smokeless tobacco or nicotine replacement therapy (NRT), current drug or alcohol abuse, afternoon expired carbon monoxide (CO) level < 10 ppm (Vitalograph Inc., Lenexa KS), breath alcohol level (Alert breathalyzer; Columbia Laboratory Supplies), or urine pregnancy test. The study was approved by the institutional review boads of the Medical University of South Carolina and the Univeristy of South Carolina. Participants were recruited *via* local media outlets in Columbia, SC, expressed no interest in quitting smoking, gave full written informed consent and received financial compensation for study participation.

General Study Procedures

Eligible participants underwent a brief training visit to learn and practice the inhibitory control task, complete a smoking-history questionnaire and the Fagerstrom Test of Nicotine Dependence (FTND). FTND scores ranged between 1 (low) and 9 (high) (27); and a urine cannabis screen was administered to assess recent use. Participants were tested while in a smoking satiated state during each experimental visit (i.e. < 30 min since smoking a

TABLE 1 | Subject demographics/baseline assessments.

Sample N (Female)	12 (3)
Mean age	31.42 (7.39)
Years of education	13.00 (1.35)
Smoking related variables	
Nicotine dependence (FTND)	5.42 (2.19)
Years smoking	13.83 (7.57)
Average daily cigarettes	16.42 (4.52)
Carbon monoxide (CO): Visit 1	19.50 (8.73)
Minutes since last cigarette: Visit 1	23.75 (16.11)
Carbon monoxide (CO) Visit 2	23.33 (9.20)
Minutes since last cigarette: Visit 2	15.83 (15.49)
Positive urine cannabis screen	6

Standard deviation reported in parentheses next to mean where applicable.

cigarette of their preferred brand). Participants first underwent an experimental fMRI visit during which time they performed the IC task in order to measure baseline inhibitory control task performance and identify an individual's task-related peak activation cluster in the r.IFG [BA 44 and 45: see **Figure 1**, **Table 2**]. Using a randomized, counterbalanced cross-over design, participants then returned for two separate experimental TMS visits (separated by 2–30 days) and received iTBS on one visit and cTBS on the other visit. During each of the two experimental TMS visits, all participants performed the inhibitory control task at the beginning of the session on a computer outside of the scanner. Following a 15-min break, the appropriate TBS protocol was performed and, after a 15-min delay, participants again performed the inhibitory control task on a computer outside of the scanner. The effects of TBS stimulation on inhibitory control task performance were assessed by examining changes in behavioral task performance from 15 min pre- to- 15 min post-TBS.

TABLE 2 | MNI coordinates of the peak activation in the r.IFG for each participant.

Participant	x	y	z	SubRegion
N1	52	10	5	opercularis
N2	56	20	13	triangularis
N3	53	23	3	triangularis
N4	51	12	8	opercularis
N5	55	13	8	opercularis
N6	55	12	14	opercularis
N7	55	19	13	triangularis
N8	57	15	10	opercularis
N9	57	6	8	opercularis
N10	53	14	8	opercularis
N11	53	12	3	opercularis
N12	55	13	3	opercularis

Inhibitory Control (IC) Task

The validated event-related IC task (9, 28) included randomly presented colored circles—frequent gray ("Go"; 75.4%; n=388), rare yellow ("RareGo"; 12.3%; n=65), and rare blue ("NoGo" 12.3%; n=65). Participants were instructed to use their right index finger to press a button as quickly as possible for "Go" and contextually novel "RareGo" trials and to refrain from pressing in response to contextually novel "NoGo" trials. Behavioral data were processed and analyzed consistent with our prior work with this task (9). Prior to analysis, NoGo performance was corrected by scoring NoGo trials with a null response as incorrect when the participant did not respond to the "Go" trial immediately preceding it. The rare go trials are a particularly important component of this task, as they provide a novelty detection control condition to compare with the novel inhibitory control trials.

Image Acquisition and Modeling

Imaging was performed on a 3T Siemens Prisma scanner: a high-resolution 3D MPRAGE anatomical sequence was acquired (matrix = 256, flip angle = 9°, 166 slices, 1mm isotropic voxels; whole brain BOLD contrast sensitive images were acquired using a multi-band (6) EPI sequence (60 slices, TR=800 ms, TE=30 ms, FOV=216, 2.4 mm isotropic voxels).

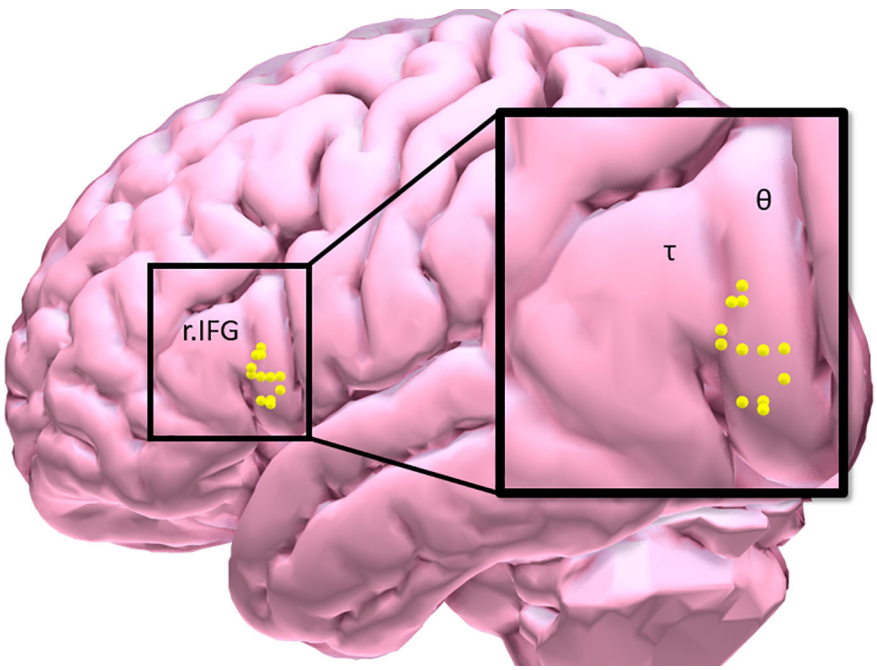

FIGURE 1 | Participant distribution of maximal inhibitory control task-related BOLD response in the right inferior frontal gyrus [τ = triangularis (n = 3); θ = opercularis (n = 9)].

fMRI IC Task Data Preprocessing

Similar to our prior analytic strategy using this task (9), fMRI data were preprocessed using SPM12 to remove noise and artifacts, motion corrected (29), temporally realigned using B-spline interpolation and smoothed with an 8 mm FWHM Gaussian filter. Functional images for each participant were processed in their native space.

IC Task Modeling

Preprocessed data were entered into a first-level, whole-brain analysis using the General Linear Model to examine BOLD response to each of the five trials of interest: $NoGo_{correct}$ (successful inhibition), $NoGo_{incorrect}$ (error of commission), $RareGo_{correct}$ (novel-target detection), $RareGo_{incorrect}$ (novel-target error of ommission), and $Go_{incorrect}$ (error of omission). Each event was modeled as a delta regressor (onset dur. = 0) and convolved with a canonical hemodynamic response function. Motion was removed through rigid body rotation and translation and parameters included as covariates. A high-pass filter (128 s; .008 Hz) was applied to remove slow signal drift. To idenitfy successful IC-BOLD response, controlling for novelty detection, a $NOGO_{correct}$–$RareGo_{correct}$ contrast image (IC-contrast) was generated (9) and fed forward to ROI identification for neuronavigation. IC task BOLD response was collected only during the baseline visit and used to inform the subsquent neuronavigation protocol (see **Figure 1**, **Table 2**).

Neuronavigation Protocol

Following the baseline scan and ROI identification procedure performed by BF (**Figure 1**, **Table 2**), neuronavigation-based TBS was administered using the Rogue Research Inc. © Brainsight system. First, co-registered anatomical and functional ROI data were entered into a participant's workflow profile. Skin and full-brain curvilinear reconstructions were created and external landmarks (bridge of nose, l.ear, r.ear) were created. Finally, the r.IFG was set as the spatial target, and the target coil trajectory was set. The same setup parameters were used across each of the two TBS visits.

Theta Burst Stimulation Protocols

Participants were randomized to receive TBS to the r.IFG on two separate experimental visits: iTBS on one visit; cTBS on one visit—counterbalanced across participants.

Determining Resting Motor Threshold

Standard procedures were used to determine the participants resting motor threshold (RMT) using parameter estimation by sequential testing (PEST) procedures (30).

Intermittent Theta Burst Stimulation (iTBS) to the r.IFG

The total duration of the iTBS protocol (21) was 190 s. Participants received stimulation over the r.IFG (a series of three-burst pulses presented at 5Hz, 10 pulses/s, 10 pulses/train, 20 trains, 10.0 s intertrain interval; 80% RMT, MagPro) using a figure 8 coil (Coil Cool B65 A/P).

Continuous ThetaBurst Stimulation (cTBS) to the r.IFG

The total duration of the cTBS protocol (24) was 34 s. Participants received stimulation over the r.IFG (an intermittent series of three-burst pulses presented at 6 Hz, 18 pulses/s, 600 pulses/train, .1 s intertrain interval; 80% RMT, MagPro) using a figure 8 coil (Coil Cool B65 A/P).

Statistical Analysis

Each of three task events of interest were modeled separately with a 2 (Time: pre, post) x 2 (Condition: iTBS, cTBS) repeated measures analysis of covariance (rmANCOVA). Though nicotine dependence severity, as measured by the FTND was not significantly associated with inhibitory control performance at any one of the measurement time-points (all p's > .05), FTND score was entered as a covariate in the rmANOVA to control for variability in this small sample. Significance was defined at α=.05. Given research suggesting cannabis use may account for significant variance in the relationship between nicotine use and inhibitory control (31), and urine drug screen (UDS) results in the current study revealing that 50% (N = 6) of the study sample tested positive for cannabis at the screening visit, baseline task performance differences between UDS outcome groups was assessed. No significant group differences were observed on task performance i.e. trial accuracy (go trials: t=.363; rare trials: t=.020; nogo trials: t =.996; all p's > .35). Therefore, UDS status was not included as a between subjects variable during hypothesis testing.

RESULTS

Blind success. The double-blind procedure used in the study was successful. Neither the participants [X^2 (2, N=12) = 1.71, p =.424] nor the researcher administering the behavioral assessments [X^2 (2, N=12) = 1.54, p =.462] were able to identify TBS conditions.

Effects of TBS on Inhibitory Control Task Performance

Inhibitory Control Trials

A significant condition x time interaction was identified on inhibitory control trials [F (1,10) = 7.27, p =.022, η^2 =.421). iTBS improved inhibitory control whereas cTBS impaired inhibitory control (iTBS: pre- M = 53.6, SE ± 4.2, post- M = 59.88 ± 3.2; cTBS: pre- M = 55.6 ± 3.3, post- M = 50.5 ± 4.7 **Figure 2A**). No significant main effect of condition or time were observed (p's > .4). Post-hoc examination of associations between baseline FTND scores and TBS induced change in inhibitory control performance (pre-post TBS Δ) failed to reveal a significant association (iTBS: p =.163; cTBS: p =.063); omitting FTND in the rmANOVA resulted in a reduction in the effect size (η^2 =.193).

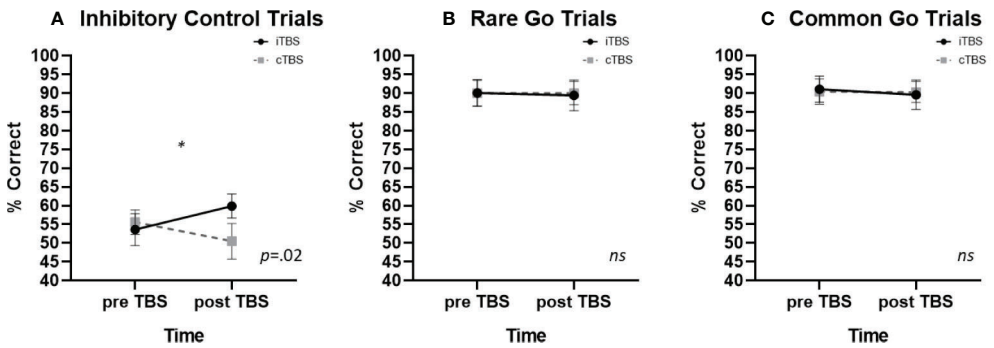

FIGURE 2 | The effects of thetaburst TMS on inhibitory control task performance (mean ± SEM) on **(A)** inhibitory control, **(B)** rare go, and **(C)** common go trials. TMS, transcranial magnetic stimulation.

Rare Go Trials

There were no significant effects of TBS on rare go trial performance. Neither the condition x time interaction (p =.932; iTBS: pre—M = 90.1 ± 3.6, post—M = 89.4 ± 4.1; cTBS: pre- M = 90.0 ± 3.4, post- M = 90.0 ± 3.1; **Figure 2B**) main effect of condition (p=.937) or main effect of time (p=.294) were significant.

Frequent Go Trials

There were no significant effects of TBS on frequent go trial performance. Neither the condition x time interaction (p=.750; iTBS: pre—M= 91.1 ± 3.5, post—M = 89.6 ± 3.9; cTBS: pre M = 90.4 ± 3.4, post M = 90.3 ± 2.8; **Figure 2C**), main effect of condition (p=.847) or main effect of time (p=.468) were significant.

DISCUSSION

Results from the current study confirm that TBS can be used to parametrically modulate inhibitory control among nicotine dependent smokers. Specifically, results from this study revealed that r.IFG iTBS significantly enhances inhibitory control, whereas r.IFG cTBS significantly attenuates inhibitory control; while neither modulated novelty detection or motor responding. The extant reports in the literature for using brain stimulation to modulate executive function have primarily focused on stimulation to the left dorsolateral PFC (32). However, there is overwhelming evidence that the r.IFG (ventrolateral PFC) is a critical cortical node in the network responsible for initiating "stop" signals related to a prepotent motor response (33), and yet there is a dearth of studies reporting on the effects of TMS in general on r.IFG and, to the best our knowledge, these findings are the first to demonstrate that non-invasive neural stimulation using iTBS to the r.IFG enhances baseline inhibitory control among individuals with a substance use disorder.

Inhibitory control—the ability to withhold a prepotent response in favor of performing context-relevant, goal-directed behavior (34)—is proposed to be carried out *via* the hyperdirect pathway composed of glutamatergic mediated excitation from the prefrontal cortex (PFC) to subthalamic nucleus (STN) and then to pallidum, in turn exerting GABAergic mediated inhibition from the pallidum to the thalamus (35). In human neuroimaging studies, evidence of these interconnections has been demonstrated with tractography (36) and functional evidence for the circuitry involvement in IC performance by combined task-based fMRI and electrocorticography (ECoG) (14), IC task-based effective connectivity (37) and lesion studies (38). This neural model is further substantiated by an effective connectivity study revealing that successful IC involves the r.IFG modulating the strength of the excitatory action of the preSMA on STN, which inhibits, *via* the pallidum, motor output from thalamus to motor cortex (37). Taken together, these findings support the existence of an inhibitory control pathway in which the r.IFG serves as a cortical mediated inhibitory command input and the thalamus serves as a final gateway prior to the motor cortex mediated output required to proactively inhibit a prepotent behavioral response.

In the context of tobacco use disorder, smokers exhibit anatomical and functional abnormalities in the r.IFG. Compared to nonsmokers, smokers exhibit less gray-matter volume (GMV) in the IFG (39–41) as well as greater r.IFG BOLD response during neurocognitive task probes of executive function (15, 17). Acute smoking abstinence further increases r.IFG BOLD response during inhibitory control (6) and other neurocognitive tasks (16–18). Abnormalities in IFG structure and function implicate a compensatory mechanism by which smokers may 'over-recruit' the r.IFG in an attempt to exert IC. Indeed, baseline inhibitory control task based hyperactivity in the r.IFG is associated with worse smoking cessation outcomes. Moreover, the strength of inhibitory control task-based functional connectivity (tbFC) between the r.IFG and thalamus (corticothalamic circuit) mediates the association between IC task performance and smoking outcomes (9). Based upon the tenet that iTBS induces LTP and strengthens network activity, these findings suggest that the observed effects of r.IFG iTBS on enhancing inhibitory control may have occurred by way of strengthening corticothalamic tbFC. Similarly, the effects of r.IFG cTBS on attenuating inhibitory control may have resulted from a weakening of corticothalamic tbFC. However,

further research is needed to directly examine the potential parametric effects of TBS on corticothalamic tbFC.

CONCLUSION AND LIMITATIONS

There is critical need for a principled examination of the neural underpinnings of the effects of TBS on inhibitory control. There is an equally pressing need to evaluate the potential of this technique for modulating inhibitory control circuits implicated in SUD-relevant behavior [however, see Liu et al. (31)]. As demonstrated for the first time here, IC is amenable to enhancement through r.IFG iTBS. The application of r.IFG iTBS to individuals with a SUD, and tobacco use disorder in particular, represents a mechanistically novel path of research, complementing and building upon prior work identifying a systems-level predictive model of relapse vulnerability (9) and with potential utility in improving smoking cessation outcomes. The rationale for selecting the r.IFG as the target region to examine the effects of TBS on IC among smokers is guided by the breadth of literature on the importance of the r.IFG in IC and our prior work with smokers that demonstrated disruption in r.IFG response during tasks probing inhibitory control (9, 15–18). However, we acknowledge that TBS to the pre-SMA—a cortical node in the corticothalamic pathway—has been shown to impact inhibitory control task performance among healthy control participants (26, 42, 43) and therefore also warrants examination in future studies. It is important to note that acute administration of nicotine is known to improve executive function in both smokers and nonsmokers (44), including novelty detection which, in addition to inhibitory control, is also subserved by that r.IFG (45). Given that r.IFG mediates both inhibitory control and novelty detection, the current study utilized a variant of the go/nogo task i.e. Go-Go/NoGo that includes a rare novel item in order to examine whether the effect of TBS to r.IFG is process general or specific to IC. Results from the current study demonstrating that r.IFG TBS parametrically modulates inhibitory control but not novelty detection are fascinating and require further investigation using both fMRI and TBS to better characterize the effects of TBS on process-dependent neurocicuitry function.

The current study sought to compare the effects of iTBS vs. an active condition—cTBS and baseline in order to test the hypothesis that TBS to the rIFG may causally modulate IC in a stimulation-dependent manner (i.e. improve following iTBS, worsen following cTBS). Though a sham condition was considered, we concluded that the sham condition adds little benefit above and beyond the active—cTBS condition (and baseline) for the purpose of testing the study hypothesis. However, future larger-scale clinical studies evaluating iTBS for improving IC and clinical outcomes among individuals with tobacco use disorder will benefit from including a sham condition as a comparator condition. Despite the limitations of the current study, including a relatively small N, brief testing period and demographic and baseline variability among the study sample, the current study results provide novel and promising early-phase evidence that rIFG iTBS may help improve IC among individuals with tobacco use disorder.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical University of South Carolina IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BF designed the study. RN-N, MG, and PM oversaw data collection and data analysis. BF was responsible for data interpretation. RN-N and BF developed the manuscript.

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Reducing Risky Alcohol Use *via* Smartphone App Skills Training Among Adult Internet Help-Seekers: A Randomized Pilot Trial

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Alcohol is one of the leading risk factors for global disease burden and overconsumption leads to a wide variety of negative consequences in everyday life. Digital interventions have shown small positive effects in contributing to reductions in problematic use. Specific research on smartphone apps is sparse and the few studies published indicate effects ranging from negative or null to small or moderate. TeleCoach™, a web-based skills training smartphone app, has shown positive effects in non-treatment-seeking university students with excessive drinking. This pilot trial aimed to evaluate app effects in a sample of internet help-seekers from the general population in Sweden. A total of 89 participants were recruited *via* online advertisement. Following baseline assessment for hazardous use, they were randomized to TeleCoach or a web-based control app offering brief information and advice regarding problematic alcohol use. The primary outcome was number of standard drinks per week; secondary outcomes included drinking quantity and frequency, binge drinking and blood alcohol count measures as well as app user data and comorbidity related to depression, anxiety, and drug use. Analysis of baseline and 6-week follow-up outcomes showed significant within-group effects on alcohol consumption but no significant between-group differences. Effect sizes for the within-group changes in the primary outcome over time were significant [$F(1, 55)=43.98$; $p < 0.001$], with a Cohen's d of 1.37 for the intervention group and 0.92 for the control group. This difference in effect sizes indicated that continuation of the study as a large randomized, controlled trial with up to 1,000 participants could be worthwhile.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT03696888.

Keywords: alcohol, mHealth, mobile phone apps, pilot trial, randomized controlled trial, risky drinking behavior

INTRODUCTION

Alcohol is one of the most commonly used and socially accepted psychoactive substances worldwide, with overconsumption leading to significant impacts not only on individual levels but also on societal levels. Indeed, World Health Organization (WHO) reports consistently show that alcohol is ranked among the top leading risk factors for the global disease burden associated with premature death and disease. In 2016, 3 million deaths worldwide were attributed to hazardous or harmful use of alcohol. A total of 132.6 million disability-adjusted life years (DALYs), were attributable to alcohol, an equivalent of 5.1% of all DALYs in the year of 2016. Injuries, cardiovascular diseases and digestive diseases resulting from harmful alcohol consumption were among the top leading factors behind alcohol-related deaths in 2016 (1). In addition to the health-related consequences of increased alcohol consumption, it also leads to major financial consequences that burden society, including an increased need of health care, increased criminality and a loss of productivity. Implementing interventions on a societal level to lower these economic burdens could potentially save hundreds of millions of dollars per year (2).

Overconsumption of alcohol can also lead to diagnosis of mild to moderate alcohol use disorder [AUD; (3)], with prevalence estimated at 8.8% in Europe (1). AUD can involve binge drinking, defined as alcohol consumption exceeding five standard units per occasion. Individuals with AUD show high comorbidity with other psychiatric disorders, particularly mood disorders, in the general population, as shown recently in Danish (4) and South Korean (5) cohorts, with the latter showing specific comorbidity with anxiety and depression disorders as well as bipolar disorder and higher risk of suicide. Although AUD is one of the most globally prevalent mental disorders, there is a large disparity between the number of people with AUD and the number actually receiving adequate treatment. This disparity, termed the treatment gap, has been estimated to be as high as 92.4% in Europe (6). Barriers to seeking help have been shown to include stigmatization, absence of trust or belief for the effectiveness of treatment and denial are among the top barriers to help seeking (7).

In Sweden, AUD prevalence is 11% for men and women combined (14.7% for men and 7.3% for women), higher than the European Region average of 8.8% (1), and the percentage of Swedish adult hazardous drinkers with high-risk consumption or at least one episode of binge drinking over the last 30 days has been identified at 31% (8). Barriers to treatment among Swedish respondents with AUD include feelings of shame and stigma, and preferred treatment should feature low-threshold access, allow for high personal autonomy, and not interfere with everyday life activities (9). Digital interventions conform to these preferences, and international research from several countries has shown small but promising overall effects in reducing problematic alcohol use (10), with small effects found for self-guided Cognitive-Behavior Therapy (CBT) programs and small to large effects for guided programs (11). An accumulating body of research in Sweden has shown the promising effects of such interventions for reducing hazardous and harmful use of alcohol (12–14) as well as diagnosed AUD among Internet help-seekers (15). Research has also indicated increased general well-being up to 1 year after participation in digital interventions for reducing alcohol use (16).

The delivery of digital interventions for general mental health issues *via* increasingly ubiquitous smartphone apps is gaining significant ground, but significant challenges exist regarding the evidence for their effectiveness (17). Indeed, of the great number of alcohol-related apps available on the market, an early review showed that very few aimed to reduce drinking (18). Among the apps that do address reduction of problematic drinking, effectiveness research is scarce and a recent systematic review identified six apps evaluated in five different studies, with only two showing positive results in reducing drinking (19). The first, A-CHESS, targets individuals during and after residential treatment for AUD, and has led to fewer days with risk-level drinking compared to controls who received treatment as usual without access to the app, up to 4 months after leaving residential treatment; users accessed the app on 41% of days and 72% pressed a panic button at least once (20). The second, TeleCoach, has been evaluated among non-treatment seeking university students with excessive drinking beyond the limit of nine/fourteen standard units per week indicated by public health recommendations; access to TeleCoach has led to lower proportions of excessive drinking and reduced quantity and frequency after six and 12 weeks compared to waitlist controls; no user data were available (21). In a secondary analysis, the TeleCoach app has also shown positive effects among a latent class of student drinkers with frequent-heavy patterns of drinking, who differed from students with hazardous drinking who reported drinking on only 1 day a week (22). Two additional smartphone apps, not included in the abovementioned review (19), have targeted adult help-seekers. One, targeting internet help-seekers with harmful levels of alcohol use (15 or more drinks/week), did not find any effects over 6 months, although some benefit appeared to occur among those who actually downloaded the app (23). A fourth smartphone app, Drink Less, evaluated among adult help-seekers with at least hazardous alcohol use who all downloaded the app, showed declines in alcohol use over time among all participants, where self-monitoring and feedback combined led to use of more app sessions (24); secondary analysis using Bayes factors showed weak evidence for an interactive combined effect of four components (normative feedback, cognitive bias retraining, self-monitoring and feedback, and action planning) yielding lower alcohol consumption (25).

Research studies on smartphone apps for reducing problematic alcohol use among adults motivated to seek help *via* the internet are clearly scarce and have not, as yet, shown any clear positive results. Prior studies of the TeleCoach app were conducted among university students directly targeted *via* e-mail (21, 22). Uncertainty regarding the feasibility of recruitment

among internet help-seekers, as well as the potential acceptability and usage levels of the two newly designed apps to be compared, motivated the analysis of initial recruitment and 6-week follow-up data as a randomized pilot trial with feasibility assessment features (26). The pilot trial was thus an analysis of the first wave of data in the already planned full, randomized, controlled trial (RCT). The primary research question concerned comparison of the two apps in terms of indications of effects on past week drinking, with secondary outcomes measuring alcohol consumption in terms of drinking quantity and frequency, binge drinking and blood alcohol count measures, as well as self-efficacy with regard to abstaining from drinking. Given prior limitations in reported assessment of user data for the TeleCoach app [see (21)], a second question concerned overall app use and use of app components, where the intervention and control apps were compared. In view of the known high levels of comorbidity among individuals with problematic alcohol use, a third question concerned description of participant characteristics, including assessment of depression, anxiety and drug use, as well as management of depression- and drug-related comorbidity among potential participants. If no significant changes are made in study design, the pilot interim data will be included in the main trial.

MATERIALS AND METHODS

Sample

Participants were recruited *via* Google AdWords, with a link to an online screening survey. The ads appeared among the top results for Google searches including key terms in Swedish such as "alcohol problems", "alcohol help", and "alcoholism". In the screening survey, participants received information about the possibility of winning an iPad lottery if they completed all follow-ups, at 6, 12, and 26 weeks. The sample size was based on the numbers recruited within a total data collection period of 18 weeks including 6-week follow-up.

The inclusion criteria were: age over 18, and hazardous alcohol use, defined as a score of ≥6 (women) or ≥8 (men) on the Alcohol Use Disorders Identification Test [AUDIT; (27)], with differing criteria by gender in accordance with evidence-based praxis in Sweden (28). Exclusion criteria were: severe depression, as defined by scores of >30 on the Montgomery Åsberg Depression Rating Scale (MADRS-S) and/or suicidal ideation as defined by a score of >5 on question 9 of the MADRS-S (29), and/or scores of ≥8 on the Drug Use Disorders Identification Test [DUDIT; (30, 31)]. Participants who met exclusion criteria were contacted by authors AHB or OM (both licensed psychologists) for a brief clinical interview by telephone, and offered referral elsewhere if appropriate. Participants who did not respond were excluded from the study. However, those who were interviewed and wanted to participate in the study, in spite of fulfilling exclusion criteria for the study, were allowed to participate, on condition that follow-up interviews were planned. As described above, exclusion criteria concerned high levels of self-reported depression, suicidal ideation or moderate drug use. The reasoning behind inclusion for these individuals was that interviewed participants had explained the background to their self-reports; e.g., that despite depressive symptoms they were still functioning at work and in family and social roles, that their suicidal ideation was variable and that they had no concrete plans of committing suicide, and/or that their drug use was highly sporadic or that they had misunderstood the drug questionnaire. Eleven participants who met exclusion critiera did not respond to contact attempts; five additional participants who had met exclusion criteria at baseline were included in the study after the telephone interview.

It should be noted that inclusion and exclusion criteria were amended after 2 weeks of recruitment, to conform to the above description. According to the initial study protocol, the inclusion criterion of risky alcohol consumption was defined as alcohol consumption over public health guidelines in Sweden, stipulating standard unit consumption (12 grams of alcohol) of >9 (women) or >14 (men) (32). An additional exclusion criterion required participants to meet ≥6 AUD symptoms according to the DSM-5. In combination, these criteria led to very few individuals meeting the criterion for risky alcohol consumption without also meeting the DSM-5 criterion for AUD, resulting in exclusion of most potential participants. These criteria were therefore amended to the ones described above, and approved by the Swedish Ethical Review Board 4 weeks after recruitment began (2018/2569-32). Three individuals were excluded due to meeting the AUD-criterion before the amendment was approved.

Procedure

Participants completed the screening survey after giving their informed consent. Those who did so, and met inclusion criteria (manual assessment), were referred to an online baseline assessment survey including demographic information, gender and weight data for calculation of estimated blood alcohol concentration (eBAC), and further questions on alcohol consumption, readiness to change, abstinence self-efficacy, cravings, and anxiety. After completion of the baseline survey, participants were randomized to receive either the intervention or control app, which were both web-based and accessed *via* any web browser on either smartphone or computer. Participants were randomized at a 1:1 ratio through 50 x 20 block randomization (33). Study authors were blinded to the randomization process. Participants were informed that they could be randomized to one of two different apps containing supportive measures aimed to decrease risky alcohol consumption. Six weeks following inclusion, a follow-up online survey was sent out. E-mail reminders were sent to participants beginning 1 week after non-complation of the 6-week survey. The initial procedure stipulated three reminders, but in view of the pilot nature of the initial data collection and with the aim of reducing attrition, additional weekly reminders were sent until the pilot trial cut-off date to participants who did not respond. The data reported for this trial therefore include all participants who responded by the cut-off date.

Participant recruitment began on December 4th, 2018 and continued until February 15th, 2019. The final distribution of the

6-week follow up survey occurred on March 29, 2019. All data collected by April 9, 2019 were included in this pilot study. Of the 1,643 persons who clicked on the study link to the study, 9% completed the screening survey and were assessed for eligibility (n=147). Of these, 60.5% completed the baseline assessment survey and were randomized (n=89), with 64% of these responding to the follow-up survey (n=57; 26 in the intervention group and 31 in the control group). Two participants were lost at randomization because they did not access their allocated interventions. Missing data occurred at baseline because aside from those who withdrew, did not meet original or new inclusion criteria or encountering technical issues, 42 participants who were found eligible for the study at the initial screening elected not to continue to the baseline assessment survey. At 6-week follow-up, missing data occurred because 16 participants in each group simply did not respond to our invitations to participate in the follow-up survey. **Figure 1** displays the participant flow throughout the pilot trial.

Measures

The initial screening survey included measures of risky alcohol consumption, alcohol use disorder, depression and drug use disorders. Due to the changes in inclusion and exclusion criteria described above, in this pilot study the new inclusion criterion measure of the AUDIT was part of the baseline assessment survey. The baseline assessment survey also contained measures of participant readiness to change, alcohol cravings, symptoms of generalized anxiety disorder and self-efficacy regarding the confidence to abstain from alcohol.

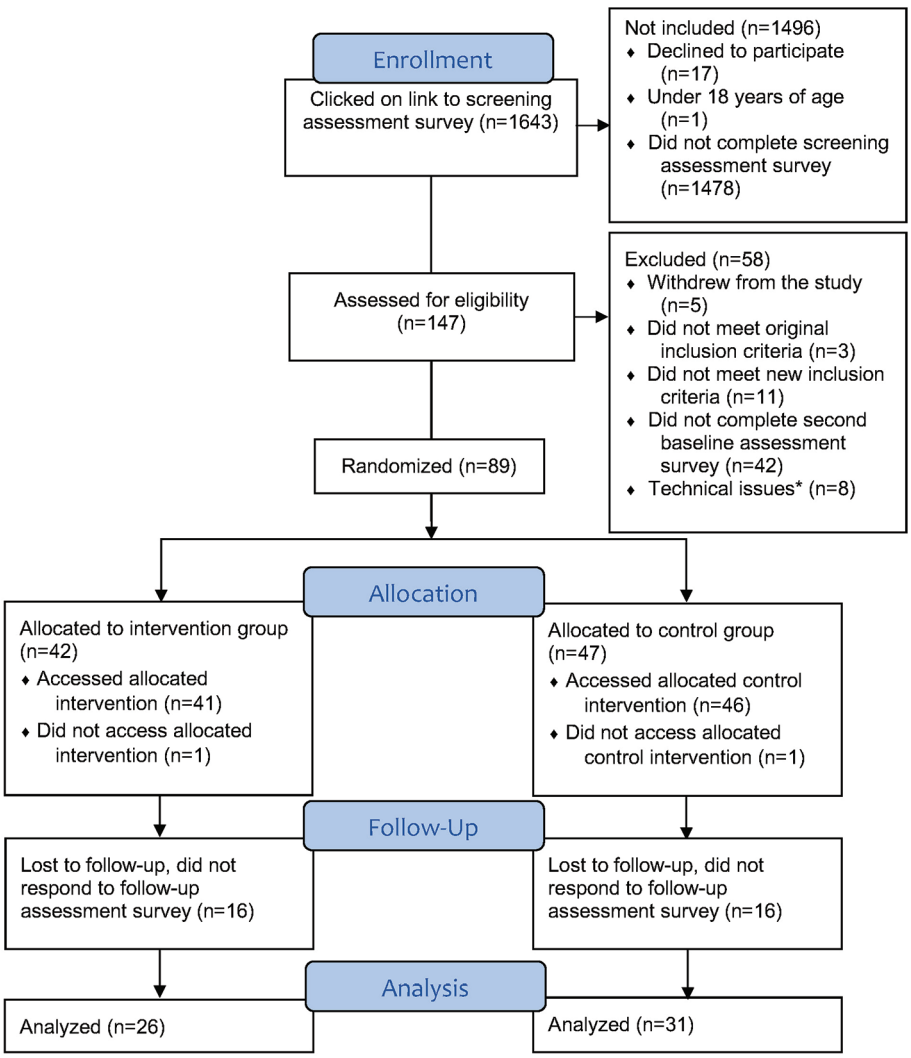

FIGURE 1 | Participant flow diagram. Completed baseline assessment survey but were not randomizeddue to entering incorrect login codes or not activating codes in time (34).

Initial Screening Survey

Timeline Followback (TLFB)

The TLFB requires respondents to report their alcohol consumption in number of standard drinks for each day for a specified period of time up to 1 year. The questionnaire is accompanied by an instruction in which respondents are presented with examples of what equals a standard glass, where they begin with reporting the day before and go backwards 1 day at a time. The TLFB has become one of the most used instruments for measuring substance consumption and its psychometric properties have been evaluated with positive results both in its standard interview administration form and in web-based administration (35–37). The version used in this study covers the past 7 days (38).

Screening for Alcohol Use Disorders (AUD)

AUD assessment was carried out *via* self-report, using 11 questions based on a validated, authorized Swedish translation of a US self-report version of the diagnostic criteria for alcohol use disorder according to the DSM-5 (39, 40).

Montgomery-Åsberg Depression Rating Scale (MADRS-S)

Depression symptoms were measured *via* the Montgomery-Åsberg Depression Rating Scale (MADRS-S), a self-rated depression scale where participants rate nine items regarding their current state of mind on a Likert scale. Each item is scored 0–6, with scores over 30 indicating risk of severe depression. Item 9 concerns suicidal ideation and scores over 5 indicate suicide risk. The psychometric properties of MADRS-S have proven to be very good (29).

The Drug Use Disorders Identification Test (DUDIT)

The 11-item DUDIT (28) was used to measure participants' problematic drug use and includes a list of common illicit drugs in different categories. Items 1–9 are scored 0–4 and items 10–11 are scored 0–2–4. Reliability and validity have been evaluated and replicated in multiple studies (41).

Baseline Assessment Survey

Alcohol Use Disorders Identification Test (AUDIT)

The 10-item AUDIT was originally developed by the WHO (26) and is a screening test for identifying hazardous drinking, based on alcohol consumption and alcohol-related problems related. Items are scored 0–4 for the first eight items and 0, 2, and 4 for the last two. The psychometric properties of the instrument have proven suitable for primary care use (28).

The Daily Drinking Questionnaire (DDQ)

In the DDQ, participants are asked to register their alcohol consumption for a typical week during the past month. In addition to registering the amount of standard drinks consumed for every day of the typical week, the time interval in which these drinks were consumed is also reported in the form of hours. Participants are also asked about the occasion in which they consumed the most alcohol during the past month and report the number of drinks and the time interval for that day. Evaluations of the psychometric properties of DDQ have shown positive results in regard to the instrument's reliability and validity (42). The DDQ yields measures of quantity, frequency, binge occasions, average estimated blood alcohol concentration (eBAC) and peak eBAC. Quantity is based on the number of standard glasses consumed in a typical week of the past month, frequency is calculated from the number of days participants consumed alcohol in the typical week, and binge occasions build on the number of reported days participants engaged in binge drinking, defined as four or more standard drinks for women and five or more for men. Average eBAC is calculated based on the Widmark formula according to the procedure described in (43) for the 7-day typical week, and peak eBAC is calculated from the event with the highest level of alcohol consumption in the past 30 days. The DDQ makes it possible to make more exact and varied calculations regarding several different parameters of alcohol consumption in a typical week in the past month, in comparison to the 7-day version of the TLFB, which describes the number of drinks in the past 7 days.

Readiness Ruler (RR)

RR consists of a Visual Analogue Scale (VAS) that measures how ready participants are to change their behavior, in this case drinking habits. Participants rated readiness to change on a scale of 0–10 ranging from "I am not ready to change my drinking habits" (0) to "I am very much ready to change my drinking habits" (10). RR is often used both clinically to facilitate behavior change in connection with Motivational Interviewing [MI; (44)] and in research to assess participant readiness for change (45).

The Penn Alcohol Craving Scale (PACS)

The 5-item PACS is a self-assessed craving scale concerning thoughts about drinking, especially the intensity and frequency of the cravings, where each item is rated 0–6. The psychometric properties of PACS have proven both valid and reliable for predicting individuals at risk for relapse into problematic drinking (46).

Generalized Anxiety Disorder (GAD-7)

The GAD-7 is a brief, 7-item self-report screening instrument for Generalized Anxiety Disorder (GAD), developed based on DSM-IV diagnostic criteria (47). Subjects are asked to rate how often they have experienced the seven GAD symptoms during the past 14 days on a scale of 0–3. Studies evaluating GAD-7 psychometric properties have provided strong support for its reliability and validity (48, 49).

The Alcohol Abstinence Self-Efficacy Scale (AASE)

The AASE measures self-efficacy regarding the self-perceived confidence in abstaining from drinking in 12 risk situations, divided into four subscales with three risk situation questions each. The subscales are termed negative affect, social positive, physical and other concerns, and withdrawal and urges. The scale has shown high levels of reliability and validity in previous studies including psychometric evaluation (50).

Outcome Measures

The primary outcome measure of alcohol consumption was the change in total number of standard drinks consumed for each of the 7 days in the preceding week, using the TLFB. Secondary outcome

measures of alcohol consumption were based on the DDQ. Six-week follow-up also included the AASE. Twelve-week follow-up (not reported here) will include the same measures as in the 6-week follow-up. The 26-week follow-up, (not reported) will include all measures from the initial and baseline screenings as well as questions on access to other treatment forms during the study (14) and questions on degree of satisfaction with the allocated app.

Intervention and Control Apps

TeleCoach

The intervention app, TeleCoach, is a smartphone app consisting of three major components, concerning self-monitoring, relapse prevention and emotion regulation. **Figure 2** shows the structure of the app with its main components and their subcomponents. Following login, users see a menu of the three main components on the home screen. Selecting any component leads to a new list of subcomponents. The three main components can be reached independently, and some sub-components are linked to each other depending on what the user has registered in the previous component.

The first component, titled "Intake and hazardous drinking", consists of two components. The first is "Register intake", consisting of a Timeline followback registration form where users report their daily drinking for the past 7 days. The second is "Hazardous drinking", where users who register excessive drinking at more than nine (women) or fourteen (men) standard drinks in the past week receive information regarding hazardous drinking and its consequences. This information is followed by a short form containing questions regarding how users perceive their own alcohol consumption as well as how motivated they feel about reducing their alcohol intake. Self-monitoring is the most commonly used component in mobile phone apps for health interventions (51). According to Albert Bandura's Social Cognitive Theory, the first step towards a behavioral change is monitoring one's pattern of behavior (52).

The second component of TeleCoach is titled "Saying no to alcohol". It consists of three parts where the first, "Risk situations", aims at identifying risk situations. Twelve questions from the AASE are answered to identify the users' potential risk situations for alcohol consumption. Based on these answers, the user is presented with proposed exercises to cope with the situations where they feel the least capable of abstaining from drinking. The second part, "Five principles" (53) offers the user five different ways of declining when offered alcohol, followed by questions concerning the user's self-efficacy for saying no. The third part, "Confident body language", provides the user with information on how to be perceived as more confident when saying no. The "Saying no to alcohol" component derives from the relapse prevention (RP) model originally developed 35 years ago by Marlatt and George (54). RP is a framework of cognitive-behavioral parts designed to facilitate behavioral change through guidance in how to handle setbacks during the process (55). RP has been evaluated through meta-analyses and shown positive effects, especially when used for alcohol-related problems. RP is a common component of conventional face-to-face interventions regarding substance use (56).

The third and final component of TeleCoach contains exercises under the title "Feel better without alcohol". This component includes three parts: "Relaxation exercises", used with the aim of teaching the user how to relax without consuming alcohol, "Positive thoughts", a training task for eliciting positive thoughts for users who often have negative thoughts about themselves, and "Coping with the urge to drink", an urge surfing technique. These three strategies focus mainly on enhancing the user's emotion-regulation skills and introduce new ways of coping with distress and cravings, replacing the use of alcohol as a stress-reducing and positive emotion enhancing tool. The relaxation exercises and urge surfing technique taught in the app are based on the theory of mindfulness, an area that has seen a dramatic increase of clinical research in the past two decades and shown positive effects on several health outcomes (57). A growing number of studies have examined the effects of mindfulness techniques on reducing stress levels and reducing cravings in recent years (58). These studies have shown promising results for the effects of both long-term and brief mindfulness interventions in treating substance misuse and enhancing relapse prevention (59, 60). "Positive thoughts", the third exercise in the "Feel better without alcohol" component, targets users who often experience having negative thoughts about themselves. This negative mindset can cause users to drink in order to cope with the negative emotions. By having the user focus on positive aspects and occurrences in their daily life the exercise aims to shift focus to a more positive mindset and evoke positive thinking. The positive thoughts

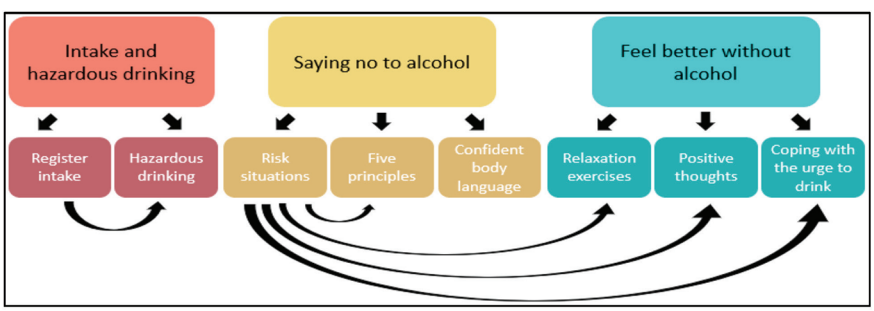

FIGURE 2 | TeleCoach app structure with component connetions.

intervention is based on the research field of positive psychology which focuses on how positive emotions, positive character traits and enabling institutions contribute to individuals' well-being (61). Using interventions in which participants are asked to think about and write down things that go well for each day has shown positive results in increasing happiness and lowering depression (62). See **Figure S1** for screenshots.

Control

The control app contains information on hazardous drinking and its consequences. The information includes early telltale signs of risk consumption as well as signs of severe risk consumption. The control app differs from the intervention app in that it does not offer the user any active components or skills training options. The information in the control app derives from the alcohol-related component in a lifestyle-improvement method evaluated in a large observational study in primary care and was used by permission (63). See **Figure S2** for screenshots.

Ethical Considerations

All participants received detailed written information about the study and gave their informed consent to participate. They were also informed that they could cancel their participation at any time without explanation. Personal data such as email address, gender and age were not stored in connection with any outcome data. All persons involved in the research project were covered by professional confidentiality. Ethical approval for the study was given by the Swedish Ethical Review Authority (approval number 2016/1088-31, amendment number 2018/2569-32).

Statistical Analyses

IBM SPSS Statistics version 25 for PC was used for all statistical analyses (64). Descriptive statistics were used to present group differences between the control and treatment group for gender, age, marital status, education, occupation, duration of alcohol problems, and previous help-seeking. For comparison of alcohol consumption measures, descriptive statistics were presented of differences in number of drinks past week, standard glasses consumed per typical week, drinking occasions per typical week, number of binge occasions per typical week, average eBAC per typical week, peak eBAC within the past month and perceived alcohol abstinence self-efficacy. Continuous variables were compared using independent samples t-tests and categorical variables were compared using chi-square tests.

Repeated measures analysis of variance (ANOVA) was used to measure changes in primary and secondary outcome measures from baseline to follow up and to examine any Group x Time interaction effects. Cohen's *d* effect sizes were calculated using an effect size calculator (65). App usage in the intervention and control participants was compared using an independent samples t-test on total number of visits, number of weeks between first and last visit, mean time per visit and total time spent using the app. Further analyses compared use of the eight TeleCoach components in the intervention group, yielding descriptive statistics regarding number of visits, mean time spent in app, total time spent in app and number of visits in each of the eight components. All app usage analyses concerned participants who had access to the app for at least a month. At the time of app usage data extraction, one participant had only had access to the app for 1 week and was excluded from these analyses.

A sensitivity analysis was performed comparing the initial screening assessment between participants who were distributed the baseline assessment survey and completed it, and those who did not complete it. The analysis showed no difference between the two groups in participant characteristics, alcohol consumption in the past week, symptoms of depression and drug usage. A sensitivity analysis was also performed for participants who completed the follow-up assessment and those who did not respond. No difference was shown in baseline participant characteristics.

RESULTS

Participant Characteristics

Participant demographic characteristics from the screening and baseline surveys are shown in **Table 1**. Participants' mean age was approximately 49 years (M = 48.93, SD = 11.88). More than two thirds of the participants were women (69.7%). A majority of the participants had a high educational level (undergraduate studies or higher, 51.7%) whereas only 6.7% of the participants had an

TABLE 1 | Participant demographic characteristics at screening and baseline assessment.

Characteristic	Controls (n=47)	Treatment (n=42)	Total (n=89)	*p* values*
Women (%)	70.20	69.00	69.70	.91
Age: *M* (*SD*)	49.43 (11.20)	48.38 (12.70)	48.93 (11.88)	.68
Marital status (%)				.95
Married	68.10	69.00	68.50	
Widowed	12.80	11.90	12.40	
Single	19.10	19.00	19.10	
Education (%)				.66
Junior high school[a]	6.40	7.10	6.70	
High school[a]	34.00	45.20	39.30	
Undergraduate[a]	51.10	33.30	42.70	
Graduate[a]	6.40	11.90	9.00	
Other	2.10	2.40	2.20	
Occupation (%)				.08
Working	93.60	73.80	84.30	
Sick leave	0.00	7.10	3.40	
Seeking	2.10	4.80	3.40	
Retired	4.30	9.50	6.70	
Parental leave	0.00	2.40	1.10	
Other	0.00	2.40	1.10	
Duration of alcohol problems (%)				.69
0–1 year	2.10	4.90	3.40	
1–2 years	27.70	26.80	27.30	
3–5 years	34.00	43.90	38.60	
6–10 years	17.00	12.20	14.80	
More than 10 years	19.10	12.20	15.90	
Help before (%)				.90
Yes	40.40	38.00	39.30	
No	59.60	61.00	60.20	

[a]*Junior high school, Primary secondary education (mandatory); High school, Upper secondary education; Undergraduate, Bachelor's level education; Graduate, Master's level education or higher. *P-values for between-group comparisons based on t-tests.*

educational level of completing junior high school. Among the 34 participants (39.3%) who had previously sought help concerning their problematic alcohol consumption, 10 had received medication such as Campral, four had attended Alcoholics Anonymous meetings and six had received psychotherapy. Another 14 participants reported seeking other forms of help, for example from their municipality or alcohol clinics.

Participants' clinical characteristics are shown in **Table 2**. Following study inclusion, participants in the intervention and control groups did not differ significantly in alcohol use disorder criteria, symptoms of hazardous drinking, alcohol cravings, or comorbidity in the form of problematic drug use, depression or anxiety. However, a significant difference did occur in participants' readiness to change, with the intervention group scoring significantly higher with a mean of 9.05 (*SD* = 1.61) in comparison to the control group, which scored 8.13 (*SD* = 2.32) with a small between-group effect size ($t(86) = 2.14$, $p = .04$, Cohen's $d = .46$).

Outcomes

Attrition

At baseline assessment, three participants had partially missing data. One participant had not filled in the DDQ at all and another had filled in the peak consumption for DDQ but not the values per day for a typical week. One final participant reported extreme values for DDQ per day but had valid data values for peak consumption for DDQ. The missing data and the extreme values were imputed using the mean values for the participant's allocated group.

At 6-week follow-up, four participants did not complete the entire 6-week follow-up survey and had valid data only for the Alcohol consumption measure of TLFB. The four participants' data were included for the analysis of variance and calculation of effect sizes for alcohol consumption. Missing data for the remaining outcome measures were not imputed.

Primary Outcome

There were no significant group differences in the primary outcome measure of alcohol consumption, measured with TLFB, at baseline or 6-week follow-up. Significant within-group decreases over time from baseline to 6-week follow-up were shown for both intervention and control groups [$F(1, 55) = 43.98$, $p < .001$]. However, the between-group Time x Group interaction effect was non-significant on alcohol consumption [*F*

TABLE 2 | Recruited participants' clinical characteristics at screening and baseline.

	Intervention		Control		Total	
Parameter (score range)	***N***	***M* (*SD*)**	***N***	***M* (*SD*)**	***N***	***M* (*SD*)**
AUD (0–11)	42	6.43 (2.37)	46	6.20 (2.37)	88	6.31 (2.36)
AUDIT (0–40)	42	18.36 (6.70)	46	18.28 (5.24)	88	18.32 (5.94)
PACS (0–30)	42	14.40 (6.24)	46	14.24 (5.92)	88	14.32 (6.04)
DUDIT (0–44)	42	0.50 (2.00)	46	0.28 (0.91)	88	0.39 (1.52)
MADRS-S (0–54)	42	16.71 (8.43)	46	15.91 (8.56)	88	16.30 (8.46)
GAD-7 (0–21)	42	6.83 (4.38)	46	5.48 (4.29)	88	6.13 (4.36)
Readiness ruler(0-10)	42	9.05 (1.61)	46	8.13 (2.32)	88	8.57 (2.05)

TABLE 3 | Baseline and follow-up primary and secondary outcome measures of alcohol consumption and abstinence self-efficacy.

Parameter	Baseline						6-week follow-up						Baseline - six-week follow-up				
	Intervention		Control		Total		Intervention		Control		Total		Within-group analysis[a]		Intervention	Control
	N	M (SD)	N	M (SD)	N	M (SD)	N	M (SD)	N	M (SD)	N	M (SD)	F (df)	*P*	Cohen's d[b]	Cohen's d[b]
Alcohol consumption	42	32.73 (21.16)	47	26.00 (14.08)	89	29.17 (17.99)	26	12.73 (10.52)	31	13.48 (11.13)	57	13.14 (10.77)	43.98 (1, 55)	<0.001	1.37	0.92
Quantity	42	26.00 (19.55)	47	22.99 (15.33)	89	24.41 (17.41)	22	11.68 (11.83)	31	13.60 (9.93)	53	12.80 (10.69)	23.01 (1, 51)	<0.001	0.87	0.71
Frequency	42	4.64 (1.68)	47	4.58 (1.69)	89	4.61 (1.67)	22	2.73 (2.31)	31	3.10 (1.85)	53	2.94 (2.04)	42.80 (1, 51)	<0.001	0.91	0.85
Binge occasions	42	3.05 (2.05)	47	2.96 (1.96)	89	3.00 (1.99)	22	1.59 (2.15)	31	1.81 (1.72)	53	1.72 (1.90)	19.39 (1, 51)	<0.001	0.72	0.57
Average eBAC	42	0.75 (0.44)	47	0.75 (0.49)	89	0.75 (0.46)	22	0.48 (0.52)	31	0.47 (0.43)	53	0.47 (0.46)	15.43 (1, 51)	<0.001	0.66	0.39
Peak eBAC	42	1.42 (0.67)	47	1.50 (0.80)	89	1.46 (0.73)	22	0.88 (0.72)	31	1.05 (0.82)	53	0.98 (0.78)	15.74 (1, 51)	<0.001	0.98	0.47
AASE total	42	2.82 (0.64)	47	2.53 (0.84)	89	2.66 (0.76)	22	2.68 (0.63)	31	2.98 (0.82)	53	2.86 (0.76)	0.88 (1, 51)	.35	0.10	0.32
AASE NA[c]	42	2.45 (0.91)	47	2.33 (1.03)	89	2.39 (0.97)	22	2.60 (1.09)	31	2.89 (1.12)	53	2.77 (1.11)	4.59 (1, 51)	.04	0.18	0.37
AASE PO[c]	42	3.24 (1.15)	47	2.91 (1.15)	89	3.07 (1.15)	22	3.15 (0.90)	31	3.22 (0.97)	53	3.19 (0.93)	0.20 (1, 51)	.65	0.04	0.08
AASE SP[c]	42	2.50 (1.00)	47	2.13 (0.98)	89	2.31 (1.00)	22	2.24 (0.90)	31	2.66 (0.93)	53	2.48 (0.93)	0.76 (1, 51)	.37	0.14	0.38
AASE WU[c]	42	3.07 (0.79)	47	2.74 (0.98)	89	2.90 (0.90)	22	2.73 (0.90)	31	3.16 (0.98)	53	2.98 (0.96)	0.22 (1, 51)	.64	0.38	0.22

[a]*Results from Repeated measures ANOVA.* [b]*Within-group effect size over time.* [c]*NA, Negative affect; PO, Physical & other concerns; SP, Social positive; WU, Withdrawal and urges.*

(1, 55) = 3.20, p =.08]. Further analyses of within-group effect sizes for alcohol consumption by time showed large effects for both the intervention (Cohen's d = 1.37) and control (Cohen's d = 0.92) groups. See **Table 3**.

Secondary Outcomes

Alcohol Consumption

The five secondary outcome measures of alcohol consumption show no significant between-group differences at baseline or 6-week follow-up, but all secondary outcome measures showed significant within-group decreases over time for both intervention and controls. Measures of within-group effect sizes showed large effects in three of the five alcohol consumption measures for the intervention group: Quantity (Cohen's d = 0.87), Frequency (Cohen's d = 0.91) and Peak eBAC (Cohen's d = 0.98); and medium effect sizes for the remaining two: Binge occasions (Cohen's d = 0.72) and Average eBAC (Cohen's d = 0.66). In the control group, one out of the five measures showed large effects: Frequency (Cohen's d = 0.85); two showed medium effect on Quantity (Cohen's d = 0.71) and Binge occasions (Cohen's d = 0.57); and the remaining two showed small effects: Average eBAC (Cohen's d = 0.39) and Peak eBAC (Cohen's d = 0.47). Nominal differences between within-group effect sizes favored the intervention group for these outcomes.

The measure of self-efficacy in abstaining from drinking showed non-significant change over time for the total score of AASE, [F(1, 51) = 0.88, p =.35]. However, out of the four subscales, a significant increase over time was seen in both groups for self-efficacy in regard to negative affect, [F(1, 51) = 4.59, p =.04]. Nominal differences between within-group effect sizes favored the control group, except for self-efficacy in regard to withdrawal urges, where the difference favored the intervention group.

App Usage

Analyses of app usage showed no significant differences between the two groups for users with access to their respective app for at least 1 month. On average, participants in the intervention group used the app for no more than 2 weeks. **Table 4** shows data on app usage, comparing the two groups.

Further analyses of app usage in the intervention group showed that out of the eight components, the "Register intake" component, in which participants complete a TLFB form, was the one most commonly used. Out of the active app components, where participants engage in different forms of exercises aimed at lowering alcohol consumption, "urge surfing" in the "Coping with the urge to drink" component was the most used. **Table 5** provides a summary of number of users and mean number of visits per component.

TABLE 5 | Number of participants accessing components and number of visits for the intervention app (see for an overview of the app).

Intervention app component	*N* (%)	Mean number of visits	*SD*
Register intake	32 (78)	1.94	1.70
Hazardous drinking	30 (73)	2.00	1.44
Risk situations	27 (66)	1.74	1.13
Coping with the urge to drink	27 (66)	1.59	1.05
Positive thoughts	25 (61)	1.56	1.16
Relaxation exercises	23 (56)	1.57	0.95
Five principles	22 (54)	1.27	0.55
Confident body language	17 (42)	1.29	0.69

DISCUSSION

Controlled trials on smartphone app studies for adult internet help-seekers with problematic alcohol use are scarce and support for app effectiveness is unclear. The overall purpose of this pilot trial was to prepare for a full randomized controlled trial by assessing possible effects on the primary outcome of number of drinks in the past week; secondary aims concerned additional alcohol outcomes, the level of app usage in intervention and control groups, and the level of participant comorbidity and establishment of routines for its management. The findings show that alcohol consumption declined with large effect sizes in both intervention and control groups, nominally favoring the intervention group but lacking between-group statistical significance. Secondary outcomes showed the same pattern, but with small to medium effect sizes. Interestingly, self-efficacy increased in relation to negative alcohol effects in both groups, nominally favoring the control group, with a small effect size. App usage data showed that both the intervention and control apps were used approximately equally, for up to 2 weeks, with an average total of four visits to the app and approximately 6 min spent per visit and a total time spent of less than 30 min. Co-morbidity levels at baseline were low regarding drug use, but the clinical severity levels of depression and anxiety were moderate. Motivation to change was very high in both groups, and significantly higher for the intervention group in comparison to the control group.

TABLE 4 | App usage data with group differences calculated via independent samples t-test.

Parameter	Intervention (n=41) M (SD)	Control (n=44) M (SD)	Total (n=85) M (SD)	*df*	*t*	*p*	*Cohen's d**
Total number of visits	3.56 (4.13)	4.39 (4.89)	3.99 (4.53)	83	-0.84	.40	0.18
Number of weeks from first to last visit	1.15 (2.31)	2.05 (2.58)	1.61 (2.48)	83	-1.69	.10	0.37
Mean time per visit (HH : MM:SS)	0:06:21 (0:05:52)	0:06:36 (0:08:59)	0:06:28 (0:07:36)	83	-0.16	.88	0.04
Total time (HH : MM:SS)	0:20:36 (0:30:17)	0:31:24 (1:03:57)	0:26:12 (0:50:35)	83	-0.98	.33	0.22

**Between-groups comparison.*

In terms of continuation with the planned large RCT, the nominally differing within-group effect sizes found in the primary outcome suggest that a larger study could be worthwhile to complete. A power analysis based on the pilot findings showed that with a significance level of α=0.05 and 80% power, a total of at least 100 participants per group will be needed at 26-week follow-up in order for the current non-significant between-group effect size of d=0.24 to be significant (see **Figure S3**). The planned baseline recruitment for the RCT has been pegged at up to 1,000 participants in total and taking attrition into account we expect to satisfy power requirements for identifying any significant between-groups effect. Even if the small and non-significant between-groups effect size identified in the pilot trial persists in the RCT, the power calculation suggests significance will be achieved, corresponding to recent results from a individual patient data meta-analysis showing an overall between-groups effect size of g=0.26 for internet-based interventions for adult problem drinking in comparison to control groups (10). An addition positive outcome of the pilot trial is the revision of inclusion criteria to include potential participants with risky alcohol use criteria according to the AUDIT and no upper limit for AUD criteria. This strategy attracted a sample with a mean AUDIT score of just over 18, indicating that participants had harmful alcohol use rather than the more severe probable dependence found in samples with more stringent inclusion criteria, in trials offering an internet intervention of at least 10 weeks [e.g., (15)].

Regarding the issues of app usage and engagement, over the 6-week pilot trial period both the intervention and control groups engaged with the app on an average of four occasions, for about 6 min each time, over a period of about 2 weeks, with an average of 26 min spent actually using the app and, surprisingly, a nominal, non-significant "advantage" for the control app. The latter app contained minimal information on reducing hazardous or harmful alcohol consumption, previously used in self-help material offered in primary care together with a behavior change counseling session (63). We would have expected intervention app users, who had access to several interactive tasks, to spend more time practicing their tasks on the app than control app users, who could basically read information and indicate their preferred behavior change tips by checking a box. Although all users had access to their respective app for at least 1 month, the mean number of weeks they actually used the app were less than two, i.e., less than half of the period available. To put these numbers in perspective, reports on smartphone usage in the UK and U.S. show that adults spend an average of 2 h and 28 min and 2 h and 22 min, respectively, per day on their smartphones (66, 67). Nonetheless, a systematic review of self-help digital devices for management of long-term conditions of ill-health showed that the time spent using app features was not related to outcome (68). The planned RCT should indicate whether the possibly greater amount of time spent on the control app persists, and may shed light on any possible advantages of the control app, which is based on informational material associated with positive health outcomes among primary care patients (63).

Comorbity is an additional factor that needs to be taken account in relation to outcomes. However, in this pilot trial our focus regarding comorbidity concerned feasibility of the screening and recruitment methods in preparation for the planned large RCT, rather than associations between comorbidity and outcomes. About one-third of the 16 participants who met comorbidity exclusion criteria responded to contact attempts and were included in the study after a telephone interview. The interview procedure was developed to begin with an explanation of the study rationale, feedback on the immediate reason for the interview in terms of particular exclusion critieria, followed by an invitation for the potential participant to describe their current situation and any existing treatment provider contacts for the depression, suicidality, or drug use identified. A brief MI-based intervention followed, where the respondent was asked how confident they were regarding change in their alcohol consumption and whether they had taken any steps to make changes, followed by a motivational summary of the next steps for reducing problematic alcohol use and/or addressing mental health or drug treatment needs. At the end of the interview, the function of potential study participation in relation to the participant's situation was discussed, information about coming telephone interviews at 6-, 12-, and 26-week follow-ups was given, and information about the National Alcohol Helpline was also given in case the user felt a need for more in-depth MI-based assistance. All telephone interviews in the pilot trial led to participant inclusion. Participants included despite comorbidity were retained for analysis in the results of this pilot trial cohort but will be analyzed separately in the large planned RCT, for possible inclusion in the main cohort but also to assess special needs, app usage and outcomes in this group. This analysis will have an exploratory character, as comorbidity may be associated with difficulty in changing behavior, but the motivational support offered in this study to participants with comorbidity may facilitate change in comparison to participants without comorbidity who did not receive such support.

Strengths and Limitations

This pilot trial had several strengths, including low threshold access for internet help-seekers with at least hazardous alcohol use, measurement of app usage, and attention to comorbidity and development of a procedure to address it within the trial. Given that 60% of the participants in the trial reported not having sought help earlier to reduce their alcohol consumption, it could be that this type of highly motivated individuals could easily be reached by the app-based intervention, eventually facilitating treatment-seeking behavior if needed following app access, and thus potentially narrowing the treatment gap for alcohol problems. Low-threshold interventions of this sort and the anonymity offered to users are two factors that may help reduce these barriers.

One possible limitation is that the study attracted participants with harmful alcohol use, on average, but also included participants with hazardous use as well as probable dependence. Problem severity could affect outcome, a

possibility we did not examine at this pilot stage but will address in the larger planned RCT. Earlier research has shown, however, that even minimal interventions can be associated with beneficial outcomes for participants at hazardous and harmful levels of use, as well as probable dependence (14). Also, some technical limitations were identified at the pilot trial stage. One technical limitation was that two participants reported difficulties in accessing the app, a factor that might be related to the web-based format of the app, which meant that it had to be saved to the user's home screen *via* the web browser, not downloaded from App Store or Google Play. This limitation was addressed by further clarification at the end of the baseline assessment survey at which point randomization to the app takes place; a general review of the instructions provided to participants has been conducted for the large RCT. A second, app-related limitation was that logon codes that were not used within 30 min of distribution were reset. Eight participants were not able to access the app they had been assigned either because they entered/saved the wrong code at the end of the baseline assessment form or not did not log in to the app in time. The time limit of the codes was not originally stated anywhere in the baseline assessment survey, but was added during the pilot study in preparation for the larger RCT. Due to regulations on data protection and privacy, participants could not use their email address as usernames for their login as this would have led to sensitive information being accessed by the app developers. Given that a randomized code must be assigned and saved by the participants, attrition due to human error is potentially higher than in trials where the trial apps are available on the App Store/Google Play (e.g., 24). A possible solution to this issue would be to create an automated email which sends the code to the user; however due to limitations in the trial survey system this was not possible to remedy

CONCLUSIONS

In conclusion, the present study shows promising results in terms of the need for continued data collection in the larger, randomized controlled trial, which in effect is a continuation of the randomized pilot study reported herein. Clearly, adult internet help-seekers are attracted by the prospect of using an app-based intervention targeting hazardous alcohol consumption. In the pilot design as well as the planned larger trial, the target sample consists of anonymous, highly motivated help-seekers. Previous studies have shown that high scores for readiness to change are associated with improved alcohol consumption patterns (45, 69). Prior research on smartphone apps targeting university students has shown that motivation is a key factor associated with positive outcomes (22); for less motivated participants Motivational Interviewing (28) has shown positive effects for university students in combination with feedback on their drinking levels (70). The reduced alcohol consumption over time noted within groups in this pilot trial is most probably mediated by participant motivation and readiness to change in addition to engagement with the respective apps, particularly in view of the restriction of the current analysis to completers of the 6-week follow-up. The interconnections between engagement, motivation, app usage, and outcomes according to an Intention-to-Treat (ITT) approach remain to be further elucidated, and the planned large RCT should contribute valuable data in this regard.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Swedish Ethical Review Authority (approval number 2016/1088-31, amendment number 2018/2569-32). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Authors AB, KS, MG, and CA conceived the study design, and MT and PT carried out the analyses within their thesis work for the BSc degree in Clinical Psychology, under AB and OM's supervision as main and co-supervisors, respectively. This manuscript, based on the thesis originally written by MT and PT, was revised and edited by AB with input from CA, OM, MG, MT, PT, and KS. All authors approved the final manuscript and are accountable for its contents.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00434/full#supplementary-material

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Conflict of Interest: AB and CA are co-owners of a company, TeleCoach AB, aiming to disseminate digital interventions for problematic behaviors including hazardous and harmful alcohol use. The company is not currently active.

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Review of the Neural Processes of Working Memory Training: Controlling the Impulse to Throw the Baby Out With the Bathwater

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Background: Smartphone technology has enabled the creation of many working memory training (WMT) Apps, with those peer-reviewed described in a recent review. WMT claims to improve working memory, attention deficits, hyperactivity and fluid intelligence, in line with plasticity brain changes. Critics argue that WMT is unable to achieve "far-transfer"—the attainment of benefits to cognition from one taught context to another dissimilar context—associated with improved quality of life. However, brain changes after a course of WMT in frontoparietal and striatal circuits—that often occur prior to behavioral changes—may be a better indicator of far-transfer efficacy, especially to improve impulse control commonly dysregulated in those with addictive disorders, yet not commonly examined in WMT studies.

Method: In contrast to previous reviews, the aim here is to focus on the findings of brain imaging WMT training studies across various imaging modalities that use various paradigms, published *via* PubMed, Scopus, Medline, and Google Scholar.

Results: 35 brain imaging studies utilized fMRI, structural imaging (MRI, DTI), functional connectivity, EEG, transcranial direct current stimulation (tDCS), cerebral perfusion, and neurogenetic analyses with tasks based on visuospatial and auditory working memory, dual and standard n-back.

Discussion: Evidence suggests that repeated WMT reduces brain activation in frontoparietal and striatal networks reflective of increased neural circuitry efficiency *via* myelination and functional connectivity changes. Neural effects of WMT may persist months after training has ended, lead to non-trained task transfer, be strengthened by auxiliary methods such as tDCS and be related to COMT polymorphisms. WMT could be utilized as an effective, non-invasive intervention for working memory deficits to treat impulse and affective control problems in people with addictive disorders.

Keywords: working memory training, neuroplasticity, n-back, CogMed, frontoparietal, striatal, addiction

INTRODUCTION

Working memory training (WMT) is a "do-no-harm" cognitive alternative (with less side effects, and greater home-based accessibility) to existing psychotherapy and pharmacotherapy for various impulse control deficits [e.g., attention deficit hyperactivity disorder (ADHD), substance use disorder, behavioral addictions and eating disorders] (1). It is proposed that WMT harnesses inherent neuroplasticity mechanisms within frontoparietal and striatal circuits, to evoke better self-regulation—via the holding in mind of cognitive strategies—over a training period of approximately 1 to 2 months (2). Extensive reviews to date examining the potential mechanisms and outcomes of WMT have concluded that most WMT paradigms are effective at "near transfer"—the ability to evoke improved performance on the trained or related task (3). However, evidence of "far-transfer"—the ability of WMT to improve cognitions and behaviors on non-trained tasks that enhance quality of life—have been less convincing, leading to the speculation that training improvements on specific WMT do not alter neural processes in a clinically relevant, long-term manner. Indeed, far-transfer of WMT to broad quality of life factors are difficult to identify, given that publications have focused predominantly on measures of working memory performance (accuracy, response times) related to attention in children with ADHD (4–7) or with Autism Spectrum Disorder (8); in adults (3, 9–14); particularly older adults (15–22). Additionally, some studies have examined the effects of WMT on dysphoria (23), cognition in children with Fragile X syndrome (24), cognition in adults with HIV (25), and football players aiming to improve their performance (26). Furthermore, the reliability and validity of brain imaging measures to quantify far-transfer effects of WMT must be examined cautiously (e.g., with advanced neuroimaging techniques, such a functional connectivity and multiple regression analyses), given the myriad of individual differences and indirect influences on vasculature function that contribute to measures of neural structure and function.

Consequently, this begs the question as to whether WMT is indeed a redundant paradigm (27) or whether it should be at least substantially revised with more advanced imaging techniques, or incorporated into other related training paradigms, such as individualized cognitive remediation therapy (28). On the other hand, one could consider whether exclusive reliance on primary outcomes associated with working memory and attention measures is shrouding the far-transfer or longevity effects of WMT, and whether the time is now ripe (before "*throwing the baby out with the bathwater*") to consider other potentially effective measures. Furthermore, perhaps, the currently accepted definition of a far-transfer effect is too narrow, in that it does not consider how distant aspects of cognitive performance and behaviors (i.e., working memory performance) might enhance seemingly unrelated functions (i.e., impulse control) which, in turn, impact quality of life (29). WMT paradigms might therefore have potential far-transfer benefits which have not been previously considered, and which might best be understood by examining the extant neuroimaging literature.

With the technology and sophisticated software that non-invasive brain imaging methods offer, uncovering neural effects is all the more feasible in populations that would benefit from non-invasive, non-pharmacological brain-focused interventions, such as those with impulse control disorders (e.g., addictions), where interventions are currently ineffective for relapse rates. As such, marked changes in activity across areas of the brain associated with specific behavior changes could infer a positive treatment outcome and far-transfer effect. For example, those with addictive disorders who often demonstrate profound deficits in impulse control, show dysfunctional frontostriatal functioning (30) with improvements in impulsivity and working memory observed within similar neural circuitry (31). That said, one could also argue that impulse control and improvements following WMT share few neural substrates, which would highlight that far-tranfer associated with impulse control is difficult to show with neuroimaging data. For example, according to the neurosynth brain imaging meta-analysis tool (neurosynth.org) a search conducted in August 2020, using the term "working memory", yielded a meta-analysis of 1,091 studies, demonstrating significant activation predominantly in the bilateral dorsolateral prefrontal cortex (DLPFC), bilateral insula, and anterior cingulate cortex. Conversely, a search using the term "impulsivity" included 120 studies and demonstrated less significant regional activation in the dorsal striatum only. Thus, it appears that working memory function is predominantly a "top-down" function associated with prefrontal cortex activation, whereas impulsivity is predominantly a "bottom-up" function associated with striatal activation. Nevertheless, despite the dissociation between these two functions, it has well been established that efficient working memory processing is associated with effective frontostriatal activity and reduced impulsivity (32–34).

According to our recent review (1) CogMed (35) WMT has the highest number of publications to date, aiming to improve the neural mechanisms underlying attention deficits in daily life and in those with ADHD (36). CogMed is a computerized, multitask, clinician-led training intervention adapted for both children and adults, as well as healthy and disordered populations—which may be a "possibly efficacious treatment" for ADHD symptoms in youth (5), but perhaps only in combination with pharmacotherapy, which is problematic for some (6). However, in a recent meta-analysis of over 750 children with ADHD engaging in cognitive training, un-blinded raters most proximal to the training session were most likely to report significant outcomes than blinded raters, therefore suggesting an experimenter bias (37). Moreover, whereas the effects on hyperactivity, impulsivity, and academic performance were not significant in the meta-analysis of Cortese et al., the near-transfer effects on working memory and related executive functions were consistent with WMT findings in other domains (and other populations not included in their meta-analysis).

Similar reviews have criticized CogMed for not sufficiently substantiating claims that WMT improves attention and ADHD symptoms (38). Furthermore, in recent reviews of the efficacy of all types of cognitive training listed on the "cognitivetraining.org" website, there is extensive evidence that brain-training interventions

improve performance on trained tasks, less evidence of improvements on closely related tasks, and little evidence that training enhances performance on distantly related tasks, or that training improves everyday cognitive performance (39). That said, there is scant evidence of specific impulse control improvements following WMT, a cognitive skill closely related to working memory and frontostriatal circuitry that is typically dysregulated in those with addictions and appetite control disorders (33).

Thus, from the perspective of current reviews and meta-analyses of WMT, it appears that the field runs the risk of becoming at worst redundant and unable to make a sustained impact on the neuroscience of mental health and enhancement of cognitive ability (27). However, other reviews—particularly of neuroimaging data—demonstrate another perspective, such as a recent paper on the effects of CogMed on neural processes (2). CogMed for those with attention deficits appears to evoke significant structural and functional changes within working memory networks and related regions, such as decreased activity in frontoparietal networks and greater connectivity between the prefrontal and parietal cortex (2). There is, however, some debate as to the effect that WMT has on brain functioning, with acute repetition training (e.g., in one session) evoking increased activation, whereas longer training durations over weeks are related to decreased activation (40–43), suggestive of priming or practice effects versus neuroplasticity effects. Moreover, there are well-known working memory capacity reductions with age, associated with reduced striatal functioning that subserve effective updating of information received (43), yet it is still not yet clear how WMT differentially effects brain functioning in younger versus older people. In addition, frontoparietal and frontostriatal circuits that are altered or made more efficient by WMT are also often dysfunctional in populations experiencing behavioral addictions (e.g., pathological gambling, excessive internet use, and eating disorders) and substance use disorders (e.g., alcohol use disorder, and stimulant misuse) (33, 44, 45), and so WMT would seem a useful non-invasive intervention to improve these neural processes. Furthermore, various psychiatric populations undergoing treatment or at risk of developing a psychiatric disorder demonstrate neurocognitive changes prior to significant behavioral or physical changes, which would support the notion that WMT may alter neurocognitive processes before behavioral far-transfer becomes apparent. In this vein, a recent WMT fMRI study of ADHD suggests that brain changes occur before significant behavioral changes (46).

Against this background, with the view that there may still be validity in pursuing WMT for treating the neural processes underlying impulse control deficits, three points are considered in this review:

a. Alternative approaches to measure the effectiveness of WMT across various training paradigms include brain imaging measures—such as structural and functional MRI—which appear to demonstrate neural changes often independently of behavioral changes that may occur later.
b. WMT research has so far relied on measures of ADHD symptoms, working memory performance (e.g., accuracy and response time), and global intelligence/executive function improvements, which critics argue do not elicit significant far transfer effects (27, 47, 48). However, exploration with various brain imaging modalities to measure WMT efficacy, particularly in relation to the neural circuitry underlying impulse control (32, 33, 49) may yield significant findings for those with addictive disorders.
c. Measures of the neural correlates of impulse control in relation to WMT in those with addictive disorders (32, 33, 37, 49) are currently scarce.

With these points in mind, the first aim of the current review is to examine all brain imaging findings across all peer-reviewed WMT paradigms since the first neuroimaging WMT study (40) to the present. The second aim is to explore the claim that there is a paucity of measurement of impulse control (associated with working memory deficits in those with addictive disorders) in neuroimaging studies of WMT. Given that near and far transfer effects on working memory, ADHD symptoms, attention, and global intelligence have been extensively reviewed elsewhere (27, 50) and that the last neuroimaging WMT review focused on CogMed (2), this review will focus on brain imaging studies across all paradigms and neuroimaging modalities. Of note, the most recent meta-analysis of WMT (not a review of neuroimaging studies) concludes that small significant and long-lasting gains occurred for working memory, which are moderated by the type of training tasks, the adopted outcome measures, the training duration, and the total number of training hours (50). Describing the outcomes of individual WMT paradigms is outside the scope of this review but can be found in various recent reviews (1, 27, 50). However, it is pertinent to note that the founder of CogMed (51) concludes that a total amount of at least 8 hours of WMT or a training period of at least 3 weeks is needed to produce significant training effects in the brain. Against this background, there is as yet no review of all WMT paradigms that have been used in neuroimaging studies of various modalities, with various populations, and so the current review addresses this gap in the literature.

METHODS

See **Figure 1** for a CONSORT diagram describing the search criteria. The following online platforms were searched for relevant articles: Google, Google Scholar, Pubmed, Medline, and ScienceDirect, with a search using the phrase "working memory training" + the name of each of the WMT paradigms included in the previous review (1). Inclusion criteria for neuroimaging studies were: a) any neuroimaging modality article written in English; b) WMT programmes supported by published peer review focusing on brain imaging methods; c) original articles and not reviews or meta-analyses (although these are referred to in text); d) publications that report the outcomes of training and not a protocol for a future WMT study; e) articles published since the first WMT brain imaging study (40) up to September 2019; f) only WMT and no other forms of cognitive training were included. Additionally, references from reviewed papers were examined.

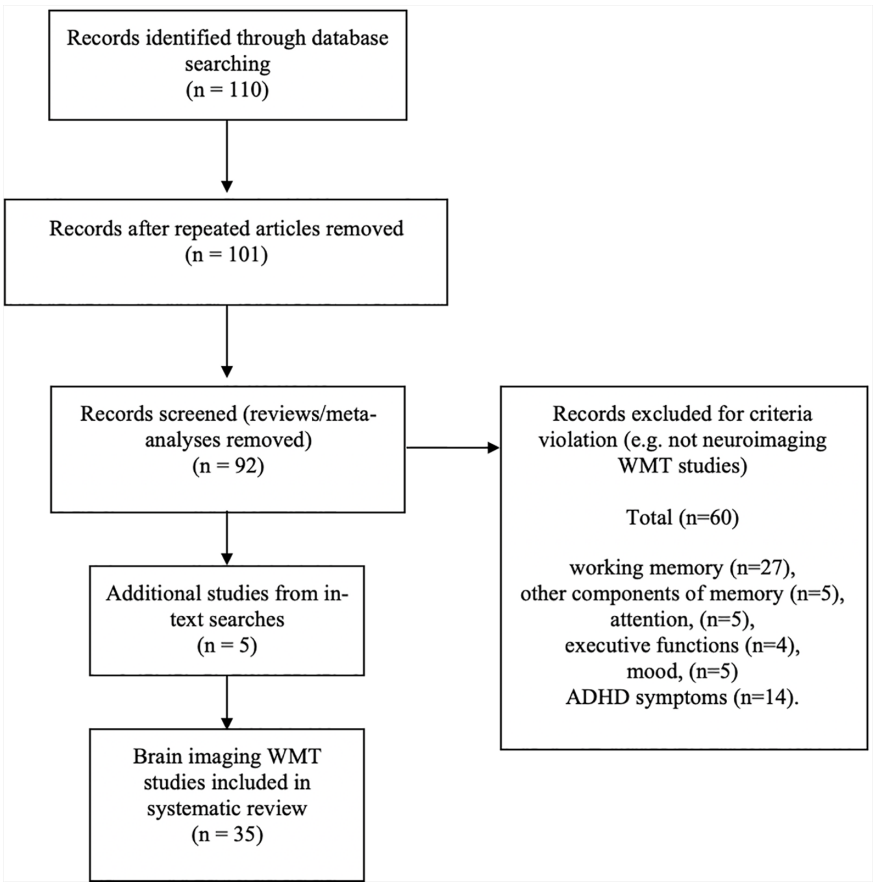

FIGURE 1 | CONSORT diagram.

RESULTS

Thirty-five neuroimaging WMT studies were found using task-based functional magnetic resonance imaging (task-based fMRI: n = 20, including 3 studies examining COMT), resting state fMRI (n = 2); structural imaging [magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and connectome voxel-based fractional ansiotrophy, n = 3], transcranial direct current stimulation (tDCS, n = 6), electroencephalography (EEG), cerebral perfusion (n = 4). WMT neuroimaging studies found in this review utilized visuospatial and auditory working memory tasks, dual or standard n-back tasks (some of which formed interventions, such as CogMed™, C-Ya™, and ACTIVATE™).

Functional fMRI

This technique is an imaging modality which measures neuronal activation by detecting changes in blood flow throughout the brain in a process termed neurovascular coupling, using a measure known as *blood oxygen level dependency (BOLD)*. When an area of the brain is active, haemodynamic activity in the region increases, enabling fMRI to measure changes in neuronal activation (52). Research with WMT has primarily relied on task-based brain activation methods, but some studies also use resting state functional connectivity methodologies which are described below.

Task-Based fMRI Studies

The majority of neuroimaging studies of WMT to date have utilized fMRI measures, currently including 18 fMRI studies. The first brain imaging study of WMT used fMRI and was conducted two decades ago by Garavan and colleagues in 2000 (40). Using a moderate or extensive short-repetition training intervention with the visuospatial delayed match-to-sample working memory task, the effects of WMT on functional neuroanatomy were examined. Decreased activation after a short period of training was reported in frontoparietal, cingulate, insular, and occipital cortex, which the authors, at this early stage of WMT research, suggested was an indication of practice effects and not neural reorganization. However, in line with two decades of subsequent neuroimaging research with various modalities, the Garavan et al. study may rather suggest improvements in neural efficiency. Landau and colleagues also observed neural deactivation after WMT in an event-related fMRI task and suggest that reduced activation in frontoparietal regions reflects greater encoding efficiency over the time course of training (42).

A potential inverted-U function was proposed to further explain the activation versus deactivation debate in WMT neuroimaging studies. This was done by another early fMRI study of WMT where the authors suggest that timing differences may occur in cerebral reorganization after WMT (41). In their study, Hempel and colleagues show increased activation in the right inferior frontal and right intraparietal cortices after two weeks of standard, increased load n-back training, but reduced activation during consolidation and after a month. Another early WMT fMRI study to examine timing effects was conducted by Olesen and colleagues (53), whereby healthy adults practiced a variety of working memory tasks for 5 weeks (tasks that would become the CogMed package), and their brain activations before, during and after training were measured. The authors reported that after training, activation increases associated with working memory were observed in the middle frontal gyrus and the inferior/superior parietal cortices. The authors argue that, whereas other studies show decreased activation following training, which may be a result of automation of cognition, practice effects, reduced cognitive load and consolidation effects over time, increased activation may rather be reflective of independence from such priming effects and new connectivity between brain regions.

However, similarly to Garavan's study (as well as later studies), Salaya and colleagues in 2006 (54) argue that in contrast to training resulting in an automatic stimulus-response association or better encoding, WMT instead relies on a continuous cognitive control process during repeated performance that leads to greater neural efficiency. In line with this suggestion, Salaya and colleagues found decreases in neural activation in both spatial and object-selective brain areas (e.g., frontal, parietal, and insular cortices) after spatial WM task repetition (and not the object-recognition task) that was independent of behavioral performance. The authors' concluded that repetition of spatial WMT in particular enabled greater neural efficiency in processing task-relevant information and improved filtering of task irrelevant stimuli. At the same time, Klingberg and colleague conducted single subject analyses using fMRI study of three subjects, to closely examine cortical reorganization over time after training with CogMed (55). The authors found that increased activation associated with WMT could be attributed to a wider recruitment of frontoparietal cortex regions during the course of training (maximum 5 weeks). Adding to the debate concerning increased or decreased activation and relative training gains, Dahlin and colleagues found, with a variable load n-back task that relative striatal activation differences between young versus older participants contributed to transfer of cognitive gain to an unrelated task (43). In other words, after 5 weeks of WMT, the study found that letter recall ability (a task unrelated to the WMT) was dependent on the degree of pre-training striatal activation, and also that older-age decline in striatal activation reduced transfer gains.

In another early fMRI study of WMT by Schneiders and colleagues in 2011 (56) the neural correlates of visual versus auditory training was examined. Greater training gains were reported with visual—as opposed to auditory—N-back (2-back), specifically in decreased activation in the right middle frontal gyrus and right posterior parietal lobe. The authors concluded that the findings suggest intra-modal but not cross-modal neural efficiency after training. Schneider and colleagues conducted another fMRI study a year later to examine whether similar effects could be observed in auditory training only, using a tonal n-back task (57). Decreased activation in the right inferior frontal gyrus and right inferior parietal lobe was again found, suggesting a cross-modal effect and reduced demand on general attentional processes after WMT, independent of behavioral performance. In a study by Schweizer and colleagues (58) participants engaged in an affective daily adaptive dual n-back task, for approximately 20 sessions between 20 and 30 min. During the task, emotionally neutral or emotionally negative faces and words were shown. Before and after the intervention, participants were scanned on the trained task at 1 back, 2 back, 3 back, and 5 back levels. During the 3-back condition, activation decreases were observed in the left dorsolateral prefrontal cortex, right superior frontal gyrus, left, and right supramarginal gyrus, left and right middle temporal gyrus, and left and right middle occipital lobe. Conversely, during the more difficult 5-back condition, activation increases were found in the right orbitofrontal cortex, right inferior frontal gyrus, and right inferior parietal cortex, suggesting neural efficiency gains at the lower cognitive load, combined with greater neural activity needed to cope with greater demands (perhaps, until the higher cognitive demands are mastered). Heinzel and colleagues in 2014 conducted a WMT fMRI study using various n-back loads to examine the sigmoid or inverted U pattern of neural activation as working memory load increases, in young versus older people (59). It has been suggested that accelerated changes in this neural pattern occur as a function of age-related changes in working memory capacity and neural efficiency. Heinzel and colleagues examined this and found increased neural efficiency and capacity after WMT, which they termed more "youth-like" brain response patterns in frontoparietal circuitry. In turn, this activation was associated with better training scores independent of the effects of age, gender, education, gray matter volume, and baseline working memory performance. In addition, reduced activation was found after training on lower cognitive loads. The authors conclude that cognitive benefits in neural activation were demonstrated in older adults who engaged in WMT with increasing loads.

Another fMRI study by the same group examined the effect that WMT has on brain activation in relation to maintaining and improving cognition in older age (60). The authors continued their investigations as to whether frontoparietal activations in older participants (between age 60 and 75 years) can be improved with WMT and related to transfer of gains to non-trained cognitive tasks. To do this, Heinzel and colleagues examined neural correlates associated with WMT transfer benefits on the untrained Sternberg delayed recognition task. It was found that WMT transfer benefits on the Sternberg task in older adults was related to decreased activation in the right lateral middle frontal gyrus/caudal superior frontal sulcus. Heinzel and colleagues conclude that their fMRI findings indicate greater processing efficiency in neural circuits supporting working memory updating ability that was able to be transferred to a delayed recall task in older adults.

Progressing this work more recently, Heinzel and colleagues examined transfer effects to a multimodal dual task, to examine whether working memory can be improved in older adults (60–72 years of age), and whether transfer gains occur across visual and auditory modalities (20). In their study, adults simultaneously completed delayed match to sample auditory or visual working memory tasks that were performed either in isolation (single-task) or in conjunction (dual task). It was found that neural activity changes in left DLPFC during one-back predicted post-training auditory dual-task performance, while neural activity changes in right DLPFC during 3-back predicted visual dual-task performance. The authors suggest that this neural activation may reflect improvement in central executive processing that could facilitate both working memory ability and dual-task coordination in older adults.

In another case study in line with Westerberg and Klingberg's study in 2007—using WMT alongside fMRI—a 38-year old man with glycogen storage disease type IV and memory complaints was given CogMed training (61). He completed CogMed over 25 sessions, with each session consisting of eight verbal and visuospatial tasks, the difficulty adjusted based on the man's daily performance over 25 weeks. The authors reported increased cortical activation in predominantly right frontoparietal regions 1–3 months after training, but both increased and decreased activation 6-months later, which particularly corresponded to improvements in auditory working memory (remembering a story), and may again be an indication of improved, long-lasting cognitive updating ability associated with greater cortical activation.

The next fMRI WMT study was published more recently in 2019, examining the neural and behavioral effects of an adaptive online verbal WMT in healthy adults with a mean age of 56 years (62). The WMT—over 4 weeks—was based on the n-back task to the maximum 9-back level (identifying when the current auditory stimulus was the same as one presented 9-items previously). The authors reported that WMT was associated with decreased activity in fronto-parieto-cerebellar circuitry, as well as limbic regions, suggesting greater efficiency with decreased activity. The training effects also extended to improvements to other working memory tasks

In another fMRI study published in 2019 (63), the effects of a 5-week single-level n-back training on brain activation in a healthy population versus a no contact control group were examined. It was found that training improved working memory accuracy and response times associated with better neural efficiency (reduced activation) that persisted 5 weeks after training in frontal superior/middle cortex, inferior parietal cortex, anterior cingulate cortex, and middle temporal cortex. In another recent fMRI study, WMT with n-back levels 0–3 back was examined as an adjunct to stimulant medication for ADHD, compared to a non-active training group (46). The authors reported decreased neural activation as working memory load increased and when comparing baseline to end of treatment (48 sessions of 30 min), in the right insula, right putamen, left thalamus, and left pallidum, and increased activation in similar regions after a comparative sustained attention task. The authors conclude that changes in brain activity may precede behavioral modifications in working memory and sustained attention, but not in inhibitory control.

Another 2019 fMRI study examined the effects of CogMed WMT on neural structure and function of children (average age almost 8 years' old) born extremely pre-term (<28 weeks' gestational age) or born with extremely low birth weight (64). Children were given CogMed for 45-min sessions, 5 days a week over 5–7 weeks and structural/functional MRI was measured at baseline and after training (versus placebo active control training). While the authors' found no significant structural changes related to WMT, they reported increased neural activation in the precuneus and posterior cingulate cortices while completing the n-back task in the scanner after CogMed training. However, the authors' concluded that these findings were not strong enough to conclude that CogMed led to significant neuroplasticity changes in children born pre-term or with extremely low birth weight.

Finally, in the most recent fMRI study (a randomized control trial), there is some evidence for the contribution of the catechol-O-methyltransferase (COMT) (Val-158/108-Met) polymorphism (rs4680) to WMT related prefrontal cortex plasticity (65). This COMT gene polymorphism results in a valine to methionine mutation, whereby three possible outcomes occur: homozygous met (met/met); homozygous Val (Val/Val) or heterozygous (Val/Met). It has been shown that the homozygous Val variant metabolizes dopamine at up to four times the rate of a polymorphism expressing the Met variant (either homo-or-heterozygous) in brain areas such as the prefrontal cortex (66). In the study by Zhao and collegues, WMT led to significantly reduced activation in the left prefrontal cortex, but especially for the Met (hetero – and homozygous) versus Val allele carriers, in that neural activation in the left prefrontal cortex of Val/Val carriers was unaltered between pre- and post-training.

In summary, the fMRI studies of WMT reveal decreased activation after WMT training in frontoparietal, cingulate, insular and occipital cortex, regions, possibly indicative of either practice effects or increased neural efficiency, for example, greater encoding efficiency over the time course of training. In addition, an inverted-U shape relationship may occur during WMT, with increased activation in the right inferior frontal and right intraparietal cortices after 2 weeks of increased load n-back training shown, but with reduced activation during consolidation and after a month of training. Furthermore, improved connectivity associated with WMT-related increased activation in middle frontal gyrus and inferior/superior parietal cortices may indicate greater functional connectivity between regions. Moreover, while the debate continues about whether reduced or increased activation signals greater neural efficiency following WMT, it is also suggested that wider recruitment of frontoparietal regions during the course of training (e.g., a maximum five weeks) is indicative of better neural functioning. Interestingly, pre-training striatal activation, and also older-age decline in striatal activation was shown to be related to reduce WMT transfer gains, and it appears that reduced activation in working memory-related brain regions most commonly reflects improved cognition, particularly in the left DLPFC, right superior frontal gyrus, bilateral supramarginal gyrus, bilateral middle

temporal gyrus, and bilateral middle occipital lobe in adults. In addition, increased neural efficiency (reduced activation) after WMT in frontoparietal regions is typical of a "young versus older" response to training, with older adults' WMT improvements related to more efficient DLPFC activation. Taken together, predominantly frontoparietal and striatal activation is associated with WMT benefits, but it is not clear whether increased or decreased activation is most significant, and how this differs in young versus older people.

Task-Based Functional Connectivity fMRI Studies

Three fMRI studies used functional connectivity analyses to examine how WMT might alter global and regional neural network activity—which is often universally consistent [e.g., default mode network, executive control network (ECN), salience network, dorsal attentional network (DAN), among others]—during fMRI cognitive task performance (67). In the first WMT functional connectivity study, Jolles and colleagues in 2011 (68) examined whether 6 weeks of adaptive WMT altered functional connectivity at rest, in 15 adults versus 9 children. The authors reported that in adults, increased functional connectivity was observed after verbal WMT, between the right medial prefrontal gyrus and other regions of the frontoparietal network, including bilateral superior frontal gyrus, paracingulate gyrus, and anterior cingulate cortex. Furthermore, children showed reduced functional connectivity between the medial prefrontal cortex and right posterior middle temporal gyrus. In addition, correlational analyses with performance changes revealed a positive link between performance increases and changes of frontoparietal connectivity, and a negative link between performance increases and changes of default network connectivity. The authors conclude that preparatory effects prior to cognitive task performance are represented in resting state networks and can be altered with training, although the degree of practice effects could not be ascertained. In a study by Sun and colleagues (69), graph theory analysis was applied to two participants who engaged in spatial n-back training for three consecutive days. The authors reported a significant decreased clustering coefficient and normalized shortest path length, suggesting a reduced local efficiency with an increased global efficiency after WM training. In another functional connectivity fMRI study of 20 WMT sessions, healthy participants were randomly assigned to either intensive dual n-back or a demanding visuospatial attention task (70). The authors reported that WMT significantly improved functional connectivity in two large-scale frontoparietal networks, namely, the ECN and the DAN. Furthermore, the magnitudes of increased functional connectivity, particularly in the DAN, correlated with cognitive intensity during the tasks and improved task performance. Thompson and colleagues conclude that these results provide insight into the adaptive neural systems that underlie large gains in working memory capacity through training.

In summary, functional connectivity studies of WMT implicate improvements (increased functional connectivity) within the ECN and dorsal attention network (DAN) in adults, but in children the ECN showed reduced connectivity following training, which may also be related to reduced reward processing in the younger group. Moreover, in an exploratory study of two participants, reduced local efficiency and increased global efficiency has been shown after WMT. These findings corroborate the task-based fMRI studies, in that both modalities implicate improvements in neural activation within prefrontal cortex networks following WMT, and while this does not demonstrate far-transfer (e.g., in relation to improvements in impulse control per se), it is worth remembering that better working memory performance is associated with reduced impulsivity (32, 33).

Resting State Functional Connectivity Studies

One pilot study of resting state fMRI (brain activation independent of task performance) used 25 sessions of 30- to 45-min CogMed training for children with neurofibromatosis type 1 (71). Neurofibromatosis is associated with significant learning and memory deficits. Following training, reduced fractional amplitude was found in the cerebellum and thalamus, and decreased regional homogeneity in the superior frontal sulcus, and increased regional homogeneity in the fusiform gyrus (a visual area). These functional brain changes corresponded to significant post-training improvements on CogMed tasks: Identification task speed and Groton Maze Learning accuracy increased.

A more recent resting state fMRI study using WMT examined the effects of computer-based training on functional connectivity of attentional networks in primary school children (72). The children with a mean age of 9 years completed two sessions per week over 13 weeks. It was found that greater functional connectivity within the attentional networks (incorporating the anterior cingulate, anterior insula, lateral prefrontal cortices, and basal ganglia) occurred after WMT. In addition, stronger functional connectivity between a right middle frontal gyrus cluster and lateral parietal/superior temporal cortices corresponded to higher inhibitory control scores.

In summary, the resting state fMRI studies link to the previously summarized fMRI studies, in that neural changes following WMT tend to occur in lateral prefrontal, parietal, and basal ganglia regions, and in these two studies to date, it appears that increased resting state activation in the attentional networks is associated with greater working memory efficiency, whereas the task-based fMRI studies show both increased and decreased activation associated with cognitive efficiency.

Structural Imaging Studies

Structural imaging techniques capture the tomography (e.g., volume, thickness, folding of gyri, and shape) of different regions of the brain, often through nuclear magnetic resonance which generates high resolution images (73). In six structural brain imaging studies (utilizing DTI, MRI, voxel-based morphometry), cortical thickness, volumetric, connectome, and white matter tractography differences have been reported after WMT. In the first structural study by Takeuchi and colleagues (74), the capacity of working memory, associated with integrity of white matter tracts in frontoparietal regions was examined using voxel-based morphometry and DTI of fractional ansiotrophy after 11 healthy participants completed: 1) Visuospatial, 2) Operational N-Back, and 3) Dual n-back WMT. The level of WMT achieved correlated with increased fractional ansiotrophy (a measure of white matter density) in

white matter regions near to the intraparietal sulcus and the anterior corpus callosum after training, suggestive of neuroplasticity/myelination changes. Takeuchi and colleagues continued their investigations by conducting a structural brain imaging study of mental calculation and working memory in 55 healthy males and females with a mean age of 21.7 years. They examined the effect of WMT on gray matter volume using voxel-based morphometry (75). It was found that mental calculations improved verbal letter span and mental arithmetic but reduced levels of creativity, and these findings were in line with volumetric reductions in the bilateral fronto parietal regions and the left superior temporal gyrus. The authors concluded that volumetric reductions also demonstrate neuroplasticity changes, perhaps in relation to greater neural efficiency and synaptic pruning of disorganized connectivity within the brain.

In another structural study, Envig and colleagues examined the plasticity effect of WMT on cortical thickness and volume in 42 male and female participants who were on average 60 years of age, after 8 weeks of intensive training using memorization techniques of location sequences throughout a person's house (76). It was found that cortical thickness changed after WMT in the right fusiform and lateral orbitofrontal cortex, which correlated positively with improvement in source memory performance. This suggests a possible functional significance of the structural changes that may be related to improved attentional control and visuospatial scratchpad maintenance memory enhancement.

Another structural study examined the dynamics of the human structural connectome underlying WMT (77). It was reported with graph theoretical analysis of the structural (white matter) network connectivity ("connectome") that there was increased global integration within a frontoparietal attention network following adaptive WMT (40 sessions of 45-min CogMed) compared with the nonadaptive training group. Moreover, the authors state that increased efficiency of the frontoparietal network was best captured with connection strengths derived from MRI metrics that were more sensitive to differences in myelination than previously used diffusion (fractional anisotropy or fiber-tracking recovered streamlines).

In another structural brain imaging study of WMT using MRI and voxel-based morphometry, in-patients with chronic methamphetamine use who were abstinent for at least one week prior to the intervention, were given 20 half an hour sessions over 4 weeks of the C-Ya App (based on 0- to 3-back of the N-back task), and were scanned at baseline and after 4 weeks (33). Compared to a treatment as usual only group who were also scanned, the WMT group showed increased bilateral basal ganglia volume that corresponded to improvements in self-reported impulsivity and self-regulation. The authors suggest, in line with previous studies (43) that increased function of the striatum is associated with better working memory ability (e.g., updating of information, effective maintenance of cognitive strategies independent of external stimulation).

In another structural imaging study of adaptive WMT, white matter plasticity in the main frontoparietal tract, namely, the superior longitudinal fasciculus, compared to the cingulum bundle as a control, was measured in line with potential cognitive benefits (78). The authors reported that white matter diffusivity changes—reflecting better working memory capacity—were specifically observed in the right dorsolateral superior longitudinal fasciculus and the left parahippocampal cingulum. Specifically, the changes were shown as increases in R1, restricted volume fraction, fractional anisotropy, and reduced radial diffusivity. Interestingly, the opposite pattern of changes in white matter microstructure was observed in the non-adaptive control session. The authors conclude that the changes are consistent with new microstructural myelination following WMT.

In summary, structural brain imaging studies of WMT have demonstrated increased white matter density within the intraparietal sulcus and the anterior corpus callosum after training (potentially an indication of increased myelination/neuroplasticity). Other studies found volumetric reductions in the bilateral frontoparietal regions and left superior temporal gyrus, which may indicate synaptic pruning underlying greater neural efficiency. In addition, increased cortical thickness in the right fusiform and lateral orbitofrontal cortex have been observed in people with an average age of 60, suggesting improvements in attentional control. And in line with fMRI studies, connectome analyses of mictrostructural changes after WMT reveal increased global integration within a frontoparietal attention network, indicative of greater neuronal efficiency. Moreover, in line with some fMRI studies, increased bilateral basal ganglia volume after WMT in people treated for methamphetamine addiction is associated with improvements in impulsivity and self-regulation. Finally, white matter plasticity (e.g., diffusivity changes) in the main frontoparietal tract, namely, the superior longitudinal fasciculus, compared to the cingulum bundle as a control, was shown to occur following WMT. Thus, in conjunction with fMRI studies, structural imaging studies confirm the involvement of frontoparietal and striatal changes following WMT.

Transcranial Direct Current Stimulation (tDCS)

This method applies low-level, continuous electrical currents delivered *via* electrodes across the scalp. Historically, tDCS was introduced to treat depression and other mood related conditions, but has since garnered attention due to some success delivering specific cognitive gains (79). To date, six studies have examined the effects of tDCS on neural activation during WMT. Mounting evidence suggests that tDCS can produce even greater gains than WMT alone, its mode of action consisting of applying a positive (anodal) or negative (cathodal) current *via* electrodes to an area of the brain within the working memory network (e.g., the dorsolateral prefrontal cortex) to facilitate the depolarization or hyperpolarization of neurons, respectively. In the first tDCS WMT study, Martin and colleagues gave 10 sessions of dual n-back training with active or sham tDCS versus tDCS only (80). In line with predictions, active tDCS enhanced participants' working memory accuracy (but not skill acquisition) compared to those who received sham tDCS or active tDCS only. In a follow-up study, the same group examined

the optimal timing of active tDCS to enhance WMT performance (81). Healthy participants received, in random order, 30 min of anodal tDCS to the left DLPFC immediately before ("offline" tDCS) and during performance ("online" tDCS) of a dual n-back WMT. The authors found that online tDCS was associated with most significant within-session greater skill acquisition and conclude that conducting WMT alongside active tDCS might provide greater cognitive gains than providing "offline" tDCS prior to the start of WMT.

In another tDCS study, authors' examined whether stimulation at home during 5 sessions of WMT improved older adults' cognition (82). It was found that 2 mA of tDCS induced significantly greater far transfer gains one month after training. Moreover, these cognitive gains were observed on far transfer tasks (subtract 2 Letter Span Task, automated Operation Span and a spatial and visual WM task), and stimulation was well tolerated by all participants. Of note, for the first time the authors also utilized functional near infra-red spectroscopy (fNIRS) to examine potential neural changes associated with WMT, but were unable to find conclusive evidence.

In another tDCS study by the same group a year later, the authors examined whether tDCS effectiveness is mediated by polymorphism in the Catel-O-methyl-transferase (COMT val158) gene (83). The authors found that those with the val/val COMT genotype gained most from 1.5 mA tDCS during visual WMT and from 1 mA tDCS during spatial WMT. For met/met polymorphisms, 2 mA resulted in significantly poorer performance compared to 1.5 mA on spatial WMT. The authors' concluded that variations in COMT val158met may predict the nature of WM improvement after initial and longitudinal tDCS. It is important to note that in the previous fMRI study that examined the contribution of COMT polymorphisms to WMT-related neuroplasticity, it was conversely found that neural activation in the val/val polymorphism group was least influenced by training (65). The discrepancy between the two studies could be due to the differences associated with encouraging neuroplasticity effects *via* WMT, versus brief neurostimulation *via* tDCS. However, more studies need to be conducted to ascertain how COMT polymorphisms are linked to WMT and prefrontal cortex function.

In another tDCS study, Jones and colleagues attempted to better understand how tDCS creates cognitive gains reflected in brain function when coupled with WMT (84). To this aim, EEG recordings were taken before and after a week of visuospatial WM change detection training, during which participants completed four sessions of frontoparietal tDCS (active anodal or sham). It was found that those who had anodal tDCS experienced greater improvement on the WMT, compared to sham tDCS, and that this improvement was reflected in frontal-posterior alpha band power, and theta and low alpha oscillations associated with greater neural synchronization.

In the most recent tDCS study of WMT, the effects of neurostimulation on working memory function in older adults, with a mean age of 74 years, were examined (85). The study used N-back training (2-back versus 0-back) over 10 sessions and found that active versus sham tDCS produced significantly increased connectivity between the left DLPFC and right inferior parietal lobe. The authors suggest that this demonstrates a method to remediate cognitive decline in older age.

In summary the tDCS studies of WMT demonstrate that active tDCS appears to enhance participants' working memory accuracy (but not skill acquisition). Moreover, online tDCS (e.g., given during WMT) appears to be associated with most significant skill acquisition, suggesting that conducting WMT alongside active tDCS might provide greater cognitive gains than providing "offline" tDCS (e.g., prior to the start of WMT). In addition, it appears that a greater level of stimulation (e.g., 2 mA tDCS) induces significantly greater far transfer gains. Genotype effects on the efficiency of tDCS during WMT show that the val/val versus met/met COMT genotype may gain the most from 1.5 mA tDCS during visual WMT and from 1 mA tDCS during spatial WMT. In contrast, for met/met polymorphisms, 2 mA may be related to poorer performance compared to 1.5 mA on spatial WMT. In terms of linking tDCS to neural activation, active tDCS improvement is linked to frontal-posterior alpha band activity, and theta and low alpha oscillations associated with greater neural synchronization. Similarly, in older adults, active versus sham tDCS increases connectivity between the left DLPFC and right inferior parietal lobe. As such, the tDCS studies appear to corroborate the findings of fMRI and structural studies, in that fronto-parietal activation is improved with stimulation.

Electroencephalography (EEG)

This technique is a non-invasive, electrophysiological imaging modality which captures topographical electrical activity direct from the cortex through electrodes on the scalp (86). Three event-related potential studies using EEG have also been conducted to examine how WMT improves connectivity across brain networks. In an EEG study by Kunda and colleagues, transcranial magnetic stimulation (TMS) was used to strengthen effective connectivity—the extent to which one node or region of the cerebrum acts in tandem with another—in 30 healthy males and females. It was shown that WMT benefits are transferred to other cognitive tasks in association with more efficient frontoparietal and parieto-occipital network connectivity (87). The authors go on to state that WMT (and TMS) evokes greater efficiency within these networks to support better stimulus processing, as demonstrated by alterations in EEG individual differences associated with greater short-term memory capacity and visual search performance.

In another EEG study by Oelhafen and colleagues (88), healthy young adults were trained for three weeks with a high or low interference training version of the dual n-back task versus a passive control group. The authors' found that training transferred to an attentional test, and that this was reflected in increased P300 activation (associated with greater selective attention) in the parietal cortex during the high interference training only. Oelhafen and colleagues concluded that WMT with an interference component may have a significant effect on altering brain processes than standard low/no interference WMT.

In the latest EEG event related study of WMT using dynamic causal modeling to examine effective connectivity changes, Chen

and colleagues contrasted P300 with N160 amplitudes—the former associated with selective attention, the latter associated with detection of novelty in review and inhibitory control (89). The authors gave participants training with either a 3-back visual WMT, or a repetition practice task, and found that visual WM training altered the frontal-parietal networks, namely, the ECN and the DAN. In contrast, the repetitive practice task modulated the parietal-frontal connections underpinning P300 activation for selective attention. The authors concluded that they were able to pinpoint specific neuroplasticity changes associated with WMT.

EEG studies, in summary, have demonstrated that WMT benefits are transferred to other cognitive tasks in association with more efficient frontoparietal and parieto-occipital network connectivity—particularly the ECN and DAN—in line with findings from other neuroimaging modalities.

Cerebral Perfusion

This measurement examines the net pressure gradient leading to cerebral blood flow in the brain. One study has examined significant training effects after seven days of n-back WMT compared to an active control group in relation to changes in cerebral blood perfusion (90). WMT was associated with both training gains and cross-task transfer compared to the active control group. Moreover, the authors reported increased perfusion during WMT in selected regions, suggesting strategies employed to cope with high task demand. Additionally, the authors reported increased blood flow at rest in regions where training effects were apparent, and that rest perfusion correlated with task proficiency, suggestive of improved neural readiness to engage in the task.

Neurogenetic Analyses

Neurogenetic analyses examine how genetic variation, including genetic mutation, affects behavior and cognition. Studies have shown that a genetic variation linked to increased dopamine metabolism in the prefrontal cortex (catechol-O-methyltransferase Val158Met; COMT) amplifies age-related alterations in working memory performance. Furthermore, in younger participants, the influence of these dopaminergic genetic polymorphisms is suggested to increase as working memory load increases. On this basis, a recent fMRI study by Heinzel and colleagues compared younger and older adults' neural responses during 12 sessions of increasingly difficult adaptive n-back WMT (17). Firstly, younger adults demonstrated greater behavioral gains than older adults after WMT. Furthermore, this age-related difference in effective WMT performance was associated with decreased plasticity in older adults carrying the Val/Val COMT genotype, with no significant genetic interaction observed in younger adults. This suggests that prefrontal cortex dopaminergic synaptic plasticity associated with WMT is significantly influenced by COMT polymorphisms, particularly in older adults. Similarly, in the fMRI study by Zhao and collegues, WMT led to significantly reduced activation in the left prefrontal cortex, but especially for the Met (hetero – and homozygous) versus Val allele carriers, in that neural activation in the left prefrontal cortex of Val/Val carriers was unaltered between pre- and post-training (65). Conversely, the tDCS study examining the influence of COMT showed that those with the val/val COMT genotype gained most from 1.5 mA tDCS during visual WMT and from 1 mA tDCS during spatial WMT. For met/met polymorphisms, 2 mA resulted in significantly poorer performance compared to 1.5 mA on spatial WMT. However, more studies examining the link between genetic polymorphisms and neural far-transfer effects during WMT are needed before definitive conclusions can be made.

DISCUSSION

Explanation of Findings

The first aim of this review has been met, to demonstrate that brain imaging studies of WMT report significant neural effects often independently of behavioral changes in frontoparietal and frontostriatal circuitry. This review has also met its second aim, to demonstrate that there is a paucity of far-transfer measures of impulse control in neuroimaging studies of WMT, despite a wealth of evidence emphasizing that frontoparietal and striatal circuits not only contribute to changes in working memory function across the lifespan but are also associated with the cognitive control of impulsivity (34, 91). As such, studies examining the neural effects of WMT associated with impulse control could be a fruitful research avenue to pursue for those aiming to improve neural processes in people with addictive disorders, which often demonstrate comorbid impulse control deficits (91). This review has also highlighted that the majority of brain imaging studies of WMT have relied on fMRI—including task-based, resting state and functional connectivity analyses (with neural links to polymorphisms in the COMT *val/val* genotype). Other imaging studies have utilized structural measures, including MRI, voxel-based morphometry for volumetric analyses, shape and cortical thickness measures, and examination of myelination neuroplasticity changes in the "connectome" after WMT. In addition, some fewer studies have begun to explore the utility of brain stimulation measures (e.g., tDCS and TMS) as an adjunct to improve WMT far-transfer effects that may translate into long-term behavioral changes. Other neuroimaging studies have used EEG and cerebral blood perfusion measures. Finally, the studies in this review have highlighted three debates within the WMT neuroimaging field: a) the pattern of brain activation underlying far-transfer, b) whether WMT is associated with increased or decreased neural activation, and c) whether there are differential neural changes with WMT in younger versus older participants.

Considering the Debates

Far-Transfer to Other Cognitive Tasks and Changes in Brain Regions

Various neuroimaging studies reported—alongside neural changes—far transfer effects of WMT to other un-related cognitive domains (20, 43, 56, 60, 61, 75, 82, 87). Using fMRI, Dahlin and colleagues demonstrated significant transfer gains of an updating task (memorizing letter sequences) to working memory performance on the n-back task that was mediated by pre-training striatal activation. Takeuchi and colleagues used structural MRI to show that performance of an intensive adaptive training of working memory using mental calculations (IATWMMC) enabled transfer gains to verbal letter span and complex arithmetic ability, but

deteriorated creativity, in line with reduced brain volume in bilateral fronto-parietal regions and the left superior temporal gyrus. Schneiders and colleagues showed transfer effects for auditory but not visual WMT that corresponded to decreased activation in the right inferior frontal gyrus and right inferior parietal cortex, reflecting less demand on general attentional control processes. Kundu and colleagues found transfer gains of increasing load n-back training to short-term memory and attention processes (visual search performance on Tetris), using EEG measures that highlighted greater effective connectivity in frontoparietal and parieto-occipital networks. Heinzel and colleagues showed—with fMRI—that 12 sessions of 45-min adaptive n-back training improved performance on a delayed recognition task (Sternberg) as well as behavioral transfer to executive functioning, processing speed, and fluid intelligence, and that this transfer gain was reflected in decreased right lateral middle frontal gyrus/caudal superior frontal sulcus (Brodmann area, BA 6/8) activation. In a later fMRI study by Heinzel and colleagues, they examined whether single-task WMT alterations in neural activity might support performance in a dual-task setting. No transfer to single-task performance was found. However, costs for audio-visual dual tasks decreased at post-measurement after WMT. These cost improvements were reflected in bilateral DLPFC activation changes. In a study by Stephens and Berryhill, it was demonstrated that 2Ma of tDCS led to greater WMT transfer gains on unrelated tasks for older participants at home one month after training had ceased.

Increased or Decreased Neural Activation After WMT

The majority of fMRI studies have reported decreased activation following WMT (40–43, 46, 54, 56–58, 60, 63). Garavan and colleagues examined neural responses after WMT in five healthy participants using a delayed match-to-sample task and reported that reduced activation appears to be a consequence of practice effects. (40). However, subsequent fMRI studies over the next two decades have honed alternative explanations; such as an inverted U- shape (41) or sigmoid (59) pattern of activation, as WMT cognitive load increases (58). For example, Hempel and colleagues reported an inverse U-shaped quadratic function with a negative exponent that was significant in the right intraparietal sulcus/superior parietal lobe under the 1-back and 2-back conditions only: during training there was increased activation, whereas at the beginning and end of the training/consolidation period these regions showed reduced activation. These non-linear activation patterns—Hempel and colleagues argue—are reflective of a mediation effect of differential neuronal mechanisms during a memory-demanding task, including: a) repetition suppression, b) enhancement, and c) delay activity (92). The authors go on to explain a theory that the prefrontal and the parietal networks may have parallel functions in WMT; a stimulus and memory enhancement mechanism associated with the saliency network and prefrontal cortex activation, and an active information suppression mechanism that occurs non-consciously during stimulus repetition. These parallel neural mechanisms may explain increases and decreases in activation according to the duration and load of WMT.

Other fMRI studies have reported increased activation following WMT (43, 53, 55, 58, 61, 64). Olesen and colleagues used 3 CogMed tasks in a small sample of 8 healthy participants to evoke increased frontoparietal activations five weeks after training. Westerberg and Klingberg—again using CogMed—showed in three participants that the extent of activated cortical area within the middle and inferior frontal gyri corresponded to the extent of working memory improvements following training. Dahlin and colleagues linked increased striatal activation prior to training, to near-transfer gains. Schweizer and colleagues used a 5-week affective dual n-back training to demonstrate improved cognitive control of emotional responses, corresponding to greater activation in the frontoparietal network and subgenal anterior cingulate (an area associated with affect regulation). Finally, Lee and colleagues examined a 38-year old man—using fMRI—with glycogen storage disease type IV and memory deficits, and found that WMT improved his memory in line with increased right frontoparietal activation; however, there were both increases and decreases in this network 6-months' later corresponding to auditory working memory ability and efficient story recollection.

The significance of increased striatal activation and plasticity in the role of WMT transfer and effective training consolidation was particularly highlighted by two studies (one functional, one structural MRI). Dahlin and colleagues conducted an fMRI study to examine whether overlapping neural patterns could predict the degree of transfer to an untrained cognitive task. They used an updating task (remembering letter sequences) to demonstrate significant transfer gains to the 3-back level of the n-back task (but not to the non-updating Stroop task), the success of which was mediated by pre-training striatal activation, which was not present in older adults (43). The authors concluded that the ability to dynamically manipulate and update information during incoming stimulus processing (a key feature of working memory) was significantly associated with striatal dopaminergic gating function, a form of synaptic gating where dopamine is suppressed or facilitated in the striatum. Similarly, in a study of chronic methamphetamine users currently abstinent and engaging in cognitive-behavioral therapy, Brooks and colleagues demonstrated that 4 weeks (20 half-hour sessions) of 0-3-back WMT led to increased bilateral basal ganglia volume (incorporating the striatum) in line with improved self-reported impulse control and self-regulation (33). In line with Dahlin and colleagues' hypotheses (43) as well as others (34, 49) increased basal ganglia volume might indicate that WMT forges neuroplasticity changes, enabling more efficient updating capabilities, which support new cognitive strategies for better cognitive control of impulsivity. In line with the importance of striatal structural and functional changes after WMT, Nemmi and colleagues have recently tested the extent to which dopamine-related genes (e.g., COMT and DAT-1), striatal activation and morphology have been associated with increased working memory capacity in different ages of adolescents (93). The authors measured working memory in adolescents twice: at age 14 and 19 years and also took neural and genetic measures. They found a significant interaction between putamen size and DAT1/SLC6A3 rs40184 polymorphism,

specifically that TC heterozygotes with a larger putamen at age 14 showed greater working memory capacity at age 19. The authors go on to explain that the effect of the dopamine transporter gene (DAT- 1) polymorphism on the beneficial development of working memory was related to changes in striatal morphology. That said, given the paucity of WMT studies examining neural changes to striatal structure and function, it is too early to comment on hypotheses about WMT far transfer to improvements in impulse control, particularly in those with addictive disorders.

Neural Processes of WMT in Young Versus Older Participants

Neuroimaging studies have shown that WMT has differential effects in younger versus older participants (17, 20, 43, 46, 59, 69, 71, 82). Dahlin and colleagues suggest a neural process underlying the often reported finding that working memory capacity and efficiency worsens with age, whereby pre-training striatal function enables updating transfer gains in older people during working memory (43). Similarly, Heinzel and colleagues show that increasing-load n-back WMT enables older adults to have "youth-like" increased frontoparietal activation, with reduced activation at lower cognitive loads reflected greater neural efficacy in older participants (59). Moreover, the authors have shown that a genetic variation associated with increased dopamine metabolism in the prefrontal cortex (Catechol-O-methyltransferase: Val158Met; COMT) amplifies age-related working memory decline, in terms of decreased behavioral plasticity in older (but not younger) adults carrying the *Val/Val* genotype (17). Comparing one young adult and one older adult (32 versus 60 years of age), Sun and colleagues demonstrated functional connectivity differences using graph theory analyses (69). In both the young and older participants, improved working memory was associated with reduced local efficiency and an increased global efficiency, although the younger participant reached higher levels on the n-back task.

In line with other structural and functional connectivity studies, Sun and colleagues argue that WMT, from just a few days to months, can augment the human brain connectome, *via* synaptic plasticity and myelination changes (68, 70, 74, 75). Moreover, a tDCS study showed that greater far-transfer WMT gains could be achieved in older people using tDCS at the 2Ma frequency at home (82). Thus, while working memory capacity and efficacy is known to decline as we age, in line with degeneration within frontoparietal and frontostriatal circuits, WMT may help to delay or slow this process. However, more research is needed in this area, particularly in terms of reversing neurodegeneration associated with chronic ageing and other degenerative conditions such as chronic stimulant use disorder.

Limitations and Implications for Future Research

This review of WMT in neuroimaging studies was hampered by the variance in sample sizes across studies, ranging from one to fifty-five participants, with the majority reporting underpowered samples. In addition, while it is useful to review the neural effects of WMT from the perspective of different imaging modalities, the majority of studies utilized fMRI with considerable variation of methods (e.g., resting state, event-related, task-based block design, and functional connectivity). As such, it is difficult to form a clear conclusion as to the consensus in the field, or to conduct a useful meta-analysis of WMT brain imaging studies—which will need to be reserved for such a time that a sufficient number of comparable studies can be analyzed with Activation Likelihood Estimation (ALE) for example (94). Nevertheless, collectively, studies using fMRI, EEG, tDCS, MRI, and DTI have contributed a significant amount over the last two decades, to the debate on how WMT alters brain processes in healthy young and older adults. Given that a major strength of this review is in highlighting that various imaging modalities have replicated effects in frontoparietal and frontostriatal circuitry—these data can be used to inform WMT interventions for addictive disorders that often demonstrate dysregulation in similar brain circuitry.

CONCLUSION

The neuroimaging studies reviewed highlight a potential non-linear relationship between brain changes and far-transfer effects that may be shrouding the measurement of significant WMT benefits. Imaging studies show that training load, duration, modality, participant age, and even participant genotype can influence the effects of WMT on the brain. In addition, neural changes may only occur gradually and prior to the emergence of significant behavioral changes, hinting at the need for researchers interested in this field to control the impulse to throw the baby out with the bathwater, and to pursue other measures. This may be especially true when considering research into the neural effects of WMT for those with addictive disorders, whose enduring impulse control deficits tend to increase the likelihood of relapse. WMT is a "do-no-harm" intervention that—according to the studies reviewed here—may improve impulse control deficits associated with aberrant frontoparietal and striatal processes in people with addictive disorders.

AUTHOR CONTRIBUTIONS

SB conceived and wrote the manuscript. RM-P created the table of studies. JT helped to substantially revise the manuscript. HS helped to revise the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.512761/full#supplementary-material

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