SUMMARY STATEMENT

PROGRAM CONTACT: Will Aklin
(Privileged Communication)
Revised Date:

Application Number: 1 R01 DA

Principal Investigator

Applicant Organization: MEDICAL UNIVERSITY OF SOUTH CAROLINA

Review Group: IPTA
Interventions to Prevent and Treat Addictions Study Section

Meeting Date: 10/06/2016
Council: JAN 2017
Requested Start: 04/01/2017

Project Title: Interventions to Prevent and Treat Addictions Study Section

SRG Action: Impact Score: 43 Percentile: 32


Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 3A-No children included, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

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ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.
RESUME AND SUMMARY OF DISCUSSION: This application proposes a three-group randomized controlled trial to test the acute and long-term effects of retrieval-extinction (R-E) training on cigarette smoking; functional magnetic resonance imaging (fMRI) is included to assess the associated brain activity. Novel, theoretically-grounded non-pharmacological treatment strategies are needed to address the significant public health problem of cigarette smoking. In discussion, reviewers were enthusiastic about the innovative and mechanistic application of the retrieval-extinction paradigm and the well-qualified investigators. The scientific premise is strong and supported by very promising pilot data from the investigators with R-E training in cigarette smokers, although there was concern that the pilot data have not been published and that the wide individual variability in response to the training in previous studies is not addressed. Reviewers’ concerns centered primarily around the approach, including that the significant variability in responses introduced by the very wide age range weakens the scientific rigor, the rationale for the timing of the second fMRI scan is unclear, the use of a mock scan as a control condition is not well justified and the design is complex. Some reviewers also had significant concern that the large sample size (which necessitates a long recruitment period) is not well justified, although other reviewers found the sample size appropriate to the design. Overall, the strengths of this innovative application are somewhat offset by the weaknesses and the project has the potential for moderate impact.

DESCRIPTION (provided by applicant): Our research group recently completed a NIDA-funded study of a brief behavioral treatment that was designed to reduce the troublesome cravings that smokers encounter when they attempt to quit smoking. This intervention was based on a growing body of neuroscience studies showing that memories for prior learning can be retrieved by the presentation of cues involved in that learning. Once retrieved, the memories enter into a brief period of vulnerability, during which they can be modified, but after which they are reconsolidated (restabilized) back into long-term storage. The treatment potential of this phenomenon was initially demonstrated in a Science report in which inpatient heroin addicts were briefly exposed to cues associated with heroin use in order to prompt the heroin use memories into a vulnerable state. Once the memories were in this state, the heroin addicts received extinction training consisting of protracted exposure to heroin associated cues. It was argued that extinction would change the memories such that the cues would no longer be associated with heroin administration and reward. Remarkably, after just two sessions of retrieval-extinction training (R-E training), the investigators found that craving in response to heroin cues was substantially reduced for up to 6-months post-treatment. This effect was observed relative to a control group that received retrieval involving non-heroin cues, followed by extinction. These impressive initial findings led us to replicate and extend the study in cigarette smokers. In our study, one group of smokers received two sessions of retrieval-extinction training with smoking cues whereas a control group received the same training except that retrieval consisted of brief exposure to neutral, smoking-unrelated cues. Craving and other reactions to familiar and novel smoking cues were assessed in test sessions performed 24-hrs, 2-weeks and 1-month after intervention; smoking behavior was also assessed over 1-month follow-up. Remarkably, at 1-month follow-up, craving to both familiar and novel smoking cues was significantly lower in the group receiving R-E training vs. control. Even more striking was the 25% reduction in the number of cigarettes smoked per day in the R-E training group vs. control. Also of significance was suggestive evidence of slowed progression towards relapse in the R-E trained group. The proposed project will replicate and extend these findings by 1) increasing the dose of intervention so as to bolster the observed treatment effects, 2) employing brain imaging methods to identify patterns of brain activity uniquely associated with the intervention and potentially predictive of treatment outcome, 3) adding a control group that will enhance understanding of the effects of this treatment, and 4) extending follow-up period to more completely document the long-term effects of the intervention. Positive findings from this study could lead to brief, effective behavioral intervention to reduce the burden levied against society by smoking. Importantly, this intervention could be easily
adapted to treat addictions involving other substances and to other disorders that frequently co-occur with addictions, such as PTSD.

**PUBLIC HEALTH RELEVANCE:** In our recently completed NIDA-funded study, we found that lasting reductions in craving and smoking could be achieved with a brief behavioral intervention designed to alter memory processes underlying smoking-related nicotine addiction. The proposed project will replicate and extend these findings by 1) increasing the dose of intervention so as to bolster the observed treatment effects, 2) employing brain imaging methods to identify patterns of brain activity uniquely associated with the intervention and potentially predictive of treatment outcome, 3) adding a control group that will enhance understanding of the effects of this treatment, and 4) extending follow-up period to more completely document the long-term effects of the intervention. Positive findings from this study could lead to the development of brief therapy that will not only improve treatment outcomes for smokers, but also be used in the treatment other substance use disorders and frequently co-occurring comorbidities such as PTSD.

**CRITIQUE 1**

Significance: 2  
Investigator(s): 2  
Innovation: 3  
Approach: 7  
Environment: 1

**Overall Impact:** This is the first submission of an R01 application that is capitalizing on the finding from a recently completed R21 project of similar design and proposes to extend the prior findings by testing hypotheses about the “dose” of retrieval-extinction training that is needed, including imaging to identify the patterns of brain activity associated with the intervention, adding a control group and extending the follow-up time period. The intervention is brief, but there is a time constraint of when the extinction phase must be conducted. Strengths include a good scientific premise for the research due to preliminary evidence of success, a novel approach to using cue-reactivity in a treatment setting, the investigative team’s prior experience with this type of intervention and excellent environmental commitment. The approach is weakened due to the following elements, many of which reduce the scientific rigor: the fact that the work from the prior R21 has yet to be published, the high failure rate of this approach in the literature (due to high variability in responses or sensitivity), the lack of planned rigorous attempts to equate reduced craving with actual reduced smoking, the imprecise smoking inclusion criteria, the overly ambitious recruitment plan, two randomization sequences, the timing of the second magnetic resonance imaging (MRI) session, and the lack of demonstrating how this technique might be integrated into clinical practice among a large network of treatment services. More fundamental weaknesses include the very broad age range for inclusion, the lack of controlling for pack years of nicotine exposure, and the resultant reduction in power to be able to test that relevant hypotheses.

1. **Significance:**

**Strengths**

- The scientific premise builds on the strong relationship between memories and cue reactivity to induce a state of vulnerability that can then be subjected to extinction.
- Has a demonstrated efficacy with heroin-dependent individuals?
- A prior R21 project demonstrated a proof of concept and that reduced nicotine craving persisted for 1 month after training.
• Non pharmacological approach that eliminates peripheral side effect profiles.

Weaknesses
• While the R21 project was completed, there are no scientific publications of the results of the study or any mention in the application that a paper has been submitted for review. The application states that the study was not powered to evaluate group differences in abstinence-related milestones.
• The literature demonstrates that there is a high degree of variability of success among individual patients, reducing the generalizability of this approach.
• There is no attempt to reconcile this wide variability and thus the success rate is difficult to predict.

2. Investigator(s):
Strengths
• The Principal Investigator Dr. [redacted] is well positioned to carry out the proposed experiments as he just finished an R21 project of the same focus but on cocaine-related use disorder.
• He has a good deal of experience and funding to explore behavioral methods for smoking cessation.
• Dr. [redacted] has past and current experience in conducting large-scale clinical trials aimed at smoking cessation.
• Dr. [redacted] brings his expertise in functional magnetic resonance imaging (fMRI) to the project; he too is currently well funded to study nicotine addiction and emotional processes.
• Dr. [redacted] is a clinical psychologist and has expertise in cue induced craving for nicotine.
• Dr. [redacted] complements the team with statistics.
• In the aggregate, the investigative team is well qualified to conduct the proposed experiments.

Weaknesses
• Publication records of the key personnel are a bit lean in the last 1-2 years.

3. Innovation:
Strengths
• The application of translating the basic concept of a retrieval-extinction (R-E) paradigm to humans using the procedures outlined in the application is rather intriguing as it suggests that previously encoded memories can be altered.
• The addition of an fMRI component to track and identify the regions that are affected during the R-E training is innovative.

Weaknesses
• While the planned development of the concept includes a fundamental approach that will provide small incremental advances, the fact that there is significant individual variability in response or susceptibility to this approach challenges the scientific rigor and thus reduces the enthusiasm for the proposal.
• While adding fMRI measures are innovative, they are being used as a passive marker and not as a predictor of treatment success.
4. Approach:

Strengths

- The fundamental application of the retrieval-extinction paradigm is solid and has sound basis in the literature as well as in the hands of the investigative team.
- This approach has already been implemented by the research team.
- The proposed extension of the work by assessing the “dose”, persistence and neurobiological correlates is sound.
- The recruitment plan appears to be feasible and builds on the prior experience—adjustments in staffing have been made to ensure sufficient patient flow through the study.
- The region of interest (ROI) approach to the fMRI analysis is appropriate for the study.

Weaknesses

- The scientific rigor of the approach is weakened by the fact that the proposed age range of 18-65 is extremely broad and this alone will introduce significant variability in responses. The team will need to stratify based on age and as a result the power will be reduced.
- This same weakness applies to the lack of quantifying prior lifetime use of tobacco (i.e., such as pack years), which will increase variability.
- The inclusion criterion of needing to smoke 10+ cigarettes for three or more years is a fundamental weakness in the approach. An 18-year-old subject will have to have started smoking at age 15 while older participants could easily have started at a much later age. The fact that early onset smoking has a significant impact on brain development will add an entirely new dimension to the variable responding to the R-E approach. Furthermore, individuals who have had 50 years of smoking (the 65 year olds who started at age 15) will have had 5 decades of reinforced cues that does not equate to the much younger individuals who will be included together in the analyses. Compared to a 20-year-old, there is a lot of basic neurobiology that differs between them and thus will add considerable confounds to the data and its interpretation.
- Only a subset of participants will have a real fMRI performed—the vast majority will be subjected to a “mock” scanning procedure. This could be interpreted as either a strength or a weakness of the application depending on how important the cues associated with a real scanner are to the subjects. A mock scanner is really a device used to “habituate” an individual to the small size of the bore, acclimate them to the sounds and alleviate any fear of being in the magnet, and they are most effective in individuals who have an aversion to small spaces. It is not known how well a mock scanner serves as a “control” for active scanning.
- The fMRI session is only conducted during baseline and after the last compensated abstinence session. It is unclear how this approach will address the specific aims, especially since the fMRI sessions are presumably being conducted sometime after the R-E sessions are completed. Thus, the effects of R-E training will not be directly assessed in the magnet.

5. Environment:

Strengths

- The Medical University of South Carolina is well suited to support the proposed studies.
- The Addictive Behaviors Research Laboratory (ABRL) and the Translational Research of Addiction and Integrative Neuroscience Laboratory (TRAIN Lab) offer excellent resources for the proposed plan.
Imaging will be conducted at the Center for Biomedical Imaging and includes a 3T Siemens TIM Trio scanner.

**Weaknesses**
- None noted.

**Protections for Human Subjects:**

Acceptable Risks and/or Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):
- Acceptable
  - A DSMB will be created for this study.

**Inclusion of Women, Minorities and Children:**
- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

**Vertebrate Animals:**
Not Applicable (No Vertebrate Animals)

**Biohazards:**
Not Applicable (No Biohazards)

**Budget and Period of Support:**
Recommend as Requested

**CRITIQUE 2**

Significance: 4
Investigator(s): 2
Innovation: 2
Approach: 5
Environment: 2

**Overall Impact:** This innovative and rigorous application has a scientific premise that is based in part on what appear to be very promising pilot data recently completed by this accomplished team of investigators. The pilot data are unpublished but preliminary results in 77 subjects suggest emerging benefits of a retrieval-extinction (RE) paradigm at about 1 month, with reduction in craving and self-reported cigarettes smoked per day. The preliminary data are exciting and it is felt could make a major impact on treatment of addiction, although additional detail of the preliminary data is lacking. The environment is also conducive to completing the aims. However, the rigor of the approach is undermined by several aspects, including an overly ambitious recruitment plan that spans 49 months and threatens the ability of the team to complete the work within the required timeframe. The sample size driving this extended recruitment period is not well justified. The applicants state that clinically-relevant effect sizes are necessary at this stage of investigation, which is laudable. However, they
already demonstrated effects that have clinical relevance in a much smaller sample in the pilot work. While adding a third arm is scientifically well-justified, it is not clear how this warrants increasing the sample size four-fold. The design, while rigorous, is also complex and involves 2 randomization steps. At times it is difficult to glean all details from the text without a comprehensive study flow that is in addition to the detailed experimental paradigm visuals provided. As an example, the justification of timing for major components of the Approach, such as the 2\textsuperscript{nd} functional magnetic resonance imaging (fMRI) scan, is underdeveloped.

1. Significance:
   
   **Strengths**
   - The scientific premise for a retrieval-extinction (R-E) intervention is strong as evidenced by the investigators' completed R21 pilot (unpublished data) and bolstered by other studies using R-E interventions for different clinical populations. There are also other published data, largely from the fear literature, that support the scientific premise of the proposed work.

   **Weaknesses**
   - The investigators do not address potential criticism of the process of disrupting reconsolidation prior to extinction as an effective intervention – e.g., Klucken et al, Cortex, 2016.
   - The investigators make the case that there is a stronger scientific premise to pursue a mechanistic understanding of the pilot findings. They argue in favor of an fMRI study rather than an efficacy study using R-E as an adjunct to pharmacotherapy. This is an open question, as the existing data seem to support proceeding in either direction. This is a comment but not necessarily a weakness.
   - What is not clear from the preliminary data (Figs 2, 3, 4) is whether the same individuals who experienced a reduction in craving in response to R-E [as compared to the no-retrieval group (NR-E)] also were the same individuals who reported fewer cigarettes per day and had longer latency to relapse.

2. Investigator(s):
   
   **Strengths**
   - The Principal Investigator and team of investigators have demonstrated expertise to conduct this work.

   **Weaknesses**
   - None noted.

3. Innovation:
   
   **Strengths**
   - R-E interventions by themselves are not novel, but it is novel to approach the individual components of retrieval and extinction separately, and to apply this to a smoking population.

   **Weaknesses**
   - None noted.

4. Approach:
   
   **Strengths**
The greatest strength of the approach is the grounding in the pilot design that attempts to disambiguate retrieval and extinction components.

The study design is complex but rigorous.

Weaknesses

Without a comprehensive study flow diagram it is difficult to understand the intricacies of the design without reading it several times.

What is the purpose of the 2nd fMRI? Figure 7 indicates that there are 2 fMRI sessions. Specifically, why does the second fMRI scan occur so early in the follow up, (at day 4?). Going back to the preliminary data from the R21, the benefits of the R-E paradigm on carbon monoxide (CO) levels and cigarettes per day (cpd) did not appear to emerge until 2-4 weeks, and were most clear at 1 month. Thus, the 2nd fMRI scan, which occurs prior to 2 weeks, will not capture brain changes associated with the intervention, but instead only duplicate the function of the 1st fMRI, which is to establish brain activity that predicts clinically-relevant outcome. On the other hand, perhaps the investigators believe that there will be measurable changes in ROI that reflect the exposure of the R-E paradigm, and that these changes can be captured this early on. However, the timing is not well justified.

A major concern is the very large sample size proposed by the investigators. While there is excellent justification for the 3 arm design, the sample size within each arm is not well justified. Having chosen the path of elucidating mechanism rather than proving efficacy, the investigators then go on to propose to recruit 333 individuals and perform fMRI scans on half of these. The rationale provided is that there is a need to have a study large enough to show clinically meaningful differences in intervention groups. However, the other two clinical studies of R-E interventions cited were able to demonstrate clinically meaningful outcomes with much smaller sample sizes. This disconnect remains confusing. It is an important design weakness because the recruitment time is very long (over 4 years) which is overly ambitious, and could jeopardize the timely completion of the study. Typically, recruitment periods span 2-3.5 years for a 5-year study to allow for potential delays.

It was unclear why investigators did not include the QSU in the questionnaire battery, as its 2 factors (including 1 that probes smoking reward) may mirror psychophysiologic data demonstrating maximally decreased reward in the R-E arm. This is not necessarily a weakness, but only a comment.

Justification for excluding insula as a pre-specified ROI was not convincing, given that this region sub-serving interception has been implicated in the absence of craving following injury (i.e., insular stroke), and theoretically could be as important as other pre-specified ROI.

5. Environment:

Strengths

The institutional environment is highly conducive to this work as evidenced by the track record of the Principal Investigator and team.

Weaknesses

Potential relative dearth of potential participants and scanner facilities to accommodate the very large sample size within a more reasonable recruitment time frame of 2-3.5 years.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections
Data and Safety Monitoring Plan (Applicable for Clinical Trials Only): Acceptable

Inclusion of Women, Minorities and Children:
- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically
- Distributions justified.

Vertebrate Animals: Not Applicable (No Vertebrate Animals)

Biohazards: Not Applicable (No Biohazards)

Budget and Period of Support: Recommend as Requested

CRITIQUE 3

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 6
Environment: 1

Overall Impact: This is a five-year R01 proposing a three-group randomized controlled trial (RCT) to test the acute and long-term effects of retrieval-extinction (R-E) training on cigarette smoking. The overall aim is to address the challenging public health problem of smoking. There is a very strong scientific premise, including promising R21 pilot data with cigarette smokers from these investigators that built on seminal data from other investigators studying R-E in opioid users. The research team and environment are both outstanding and well poised to conduct the proposed work. The proposed work is innovative in a number of ways, including adding to the very small literature looking at R-E in clinical populations and using functional magnetic resonance imaging (fMRI) to explore mechanism. Overall, this is programmatic, rigorous research that follows clearly and logically from the earlier R21 results and aims to systematically advance this line of inquiry by increasing dose, adding an additional control, and extending the follow-up period. Dissemination potential appears significant given the relatively short, outpatient intervention and there is also the possibility of generalizability to the treatment of other substance use disorders. There was some question about conducting the 2nd fMRI scan 24 hours after the end of the intervention even though reductions in cigarettes per day (CPD), carbon monoxide (CO), and craving did not manifest until 2-4 weeks later; would more dramatic differences be evident if the 2nd scan were done later? It was also very unclear what purpose the mock scans would serve. The wide age range included also suggested that there may be a need to stratify on this characteristic or a related smoking characteristic like years smoking or pack years; there are no data included from the pilot that speak to this. Some smaller issues curb enthusiasm slightly (e.g., using CO ≤ 8ppm to
indicate overnight abstinence may be high given inclusion criteria is only CO ≥10ppm; abstinence cut point for cotinine not stated), but overall enthusiasm is very high.

**Protections for Human Subjects:**

Acceptable Risks and/or Adequate Protections

- The proposed research is of low risk and protections proposed are adequate.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- A DSMB will be formed to monitor the trial.

**Inclusion of Women, Minorities and Children:**

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically
- Based on recent study, women are expected to comprise 1/3 of the sample and more than 1/2 of the sample is expected to be African American. Children less than 18 y.o. will be excluded as they are unlikely to meet the smoking history requirement.

**Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Not Applicable (No Biohazards)

**Budget and Period of Support:**

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

**PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE**

**INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE**

**INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE**

**INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE**

**COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.**

Footnotes for 1 R01 DA ; PI Name:
NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.