INTRODUCTION: We are grateful for the reviews of our RO1 application, which we believe have helped us craft a substantially enhanced resubmission. Specifically, five important changes have been made: 1) high-impact publication of preliminary data that addresses several reviewer concerns, 2) reduced sample size, 3) addressed concerns about sample age range and smoking history variation, 4) modified fMRI methods are fully justified, and 5) fully addressing the inconsistencies in the literature. These changes are detailed below.

First, it was noted that although the “scientific premise is strong and supported by very promising pilot data”, the data have "yet to be published”. We are pleased to report that they have been published in JAMA Psychiatry (highest impact journal in psychiatry).

Second, the feasibility of the targeted sample size (N=333) was questioned. This sample size was derived from powering on a relapse outcome (time to 3 consecutive days of smoking ≥ 5 cigarettes), which in retrospect was an overly ambitious goal. Accordingly, we have revised the sample size estimation to focus on measures of smoking behavior (e.g., cigarettes per day or CPD) and craving. We believe this change more closely aligns the proposed project with the successful R21 while resulting in a sample size (N=249; n=83/group) that can be recruited within a 5-year project period.

Third, there were inter-related concerns about potential inflated variability due to (a) broad sample age range (18-65), (b) smoking exposure inclusion criterion of 10+ CPD for ≥ 3 years, and (c) lack of quantifying lifetime tobacco use. It is important to note that neither participant age nor years of smoking modified the published treatment effects. Nonetheless, since the age range of the R21 sample was 22-64 yrs. and only 3 individuals (3% of the sample) were under the age of 25, we have elected to narrow the proposed age range to 25-65. This change may seem minor but it mitigates concerns about confounding effects of brain development within younger participants (who are now excluded). Our primary goal is to ensure the generalizability of the findings to the vast majority of adult regular smokers. Additionally, the Approach clearly states that we will thoroughly assess smoking history in the interest of being able to derive measures of lifetime tobacco use for inclusion in data analytic models. In the R21, we used the FTND score (proxy for tobacco exposure) as a stratification variable and it, together with randomization, resulted in the groups being equivalent with respect to years smoking (measure of lifetime exposure). Consequently, we believe that the combination of randomization and stratification on FTND score will serve as a suitable means to equate the groups on lifetime tobacco exposure. Lastly, the smoking exposure inclusion criterion (10+ CPD for ≥3yrs) is retained in the interest of ensuring the sample is homogeneous with respect to recent tobacco exposure.

Fourth, there was concern about the second scan occurring too early because treatment effects were not manifested until two weeks (CPD) or 1 month (craving) after treatment. While the figure in the original proposal suggested that treatment effects on smoking did not occur until 2-weeks post-treatment, this was not actually the case. We have now included the daily CPD data (also in published article) and it clearly shows that between group differences in smoking emerge almost immediately after treatment. Since smoking behavior is a key clinical outcome, we believe this smoking data strongly justifies doing the post-treatment scan soon after treatment, as proposed. Note a relatively minor concern about our fMRI methods centered on our exclusion of the insula as a potential region of interest; it is now included in the fMRI Analysis Plan.

It was also noted that we were not imaging the R-E training (RET) sessions in real-time, a strategy that was viewed as optimal for studying the neural processes associated treatment. However, this approach introduces some practical challenges. For example, it would require each participant to receive a pretreatment scan and three treatment scans. The costs and participant burden associated with four scans made this option seem undesirable. Additionally, imaging the RET sessions would be infeasible as they involve the active manipulation of smoking cues, which cannot occur in the scanner. To overcome these problems, we propose to image the outcome of the effects of RET on important behavior change. This would allow us to identify treatment-induced changes in brain function and assess their association with clinical outcomes.

Fifth, inconsistent findings in the RET literature were not sufficiently addressed. In the revised application, the discrepancies are identified and a framework for understanding them is outlined. We are confident that our approach employs robustly efficacious training parameters.

A number of less worrisome issues are also addressed. One of these pertained to the use of a mock fMRI session. Originally, we thought that participants who were not going through the fMRI should have some type of parallel procedural experience, thereby equating all participants on variables such as experimenter contact time, etc. However, reviewers indicated there is no evidence that mock scanning serves as a control for active scanning. We concur this is the case and have eliminated this manipulation from the study procedures. Reviewers also questioned our biochemical assessment of smoking. In the case of CO, it was noted that the overnight abstinence criterion of ≤ 8 ppm may be high given that our inclusion CO criterion was ≥ 10 ppm. Accordingly, we have adopted a more stringent overnight abstinence criterion of ≤ 5 ppm. In the case of salivary cotinine, it was noted that we did not state an abstinence cutoff. Although we intend to use cotinine only as a continuous measure of smoking level, we have now included an abstinence cutoff of ≤ 15 ng/ml. Finally, the application has been updated (recent literature) and numerous other modifications have been made to enhance clarity of exposition (substantive changes indicated by "["] bracketing).