# Mechanisms of Mindfulness for Smoking Cessation

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## Materials and Methods

*Study overview and timeline*

This was a parallel-group study with equal randomization and individuals were recruited using local flyers, and Facebook ads. The project director screened participants and eligibility criteria included: (1) smoking >10 cigarettes/day; (2) <3 months of smoking abstinence in the previous year; (3) 8+ of 10 on a "Readiness-to-change" scale [1]; (4) owning a smartphone; and (5) age between 21 – 65. Participants were excluded if they reported (1) a history of serious neurological or psychiatric conditions (beyond nicotine dependence; e.g. seizure disorder, history of a stroke, schizophrenia, bipolar disorder etc.); (2) changing dose of any psychoactive medication in the past three months; (3) previous experience with mindfulness-based stress reduction or equivalent; (4) current meditation or yoga practice (>30 minutes/day for >5 days); (5) current alcohol abuse; (6) claustrophobia; (7) pregnancy; (8) MRI incompatibility; or (9) tested positive for illegal psychoactive substances or cannabis. All participants underwent informed consent procedures prior to participation, and their participation was voluntary. Participants were given $25 upon completion of the first functional Magnetic Resonance Imaging (fMRI) visit and $75 upon completion of the second visit. This study was approved by the Institutional Review Board of the University of Massachusetts Medical School (UMMS).

At baseline, eligible participants performed a smoking cue-reactivity fMRI task at UMMS. They were then given a sealed envelope with their random assignment: an app-based MT or active control app. This was generated in variable blocks of 4 and 6 by an

independent statistician and the envelopes were prepared by an individual independent of data acquisition. An experimenter helped install the assigned app on their smartphone immediately following the first MRI visit, while making sure the participant understood the features of the app and could demonstrate how to use it. Participants were instructed to use their app to help them quit smoking over the next 4-week period. At the post-treatment visit, participants completed the same cue-reactivity task as baseline. Smoking status was verified with a carbon monoxide breathalyzer test at each visit.

*Smartphone-based App Interventions*

The app-based MT program is a phone app designed to deliver core elements of a manualized MT program for smoking cessation with high fidelity [2,3]. The program has 22 unique learning modules (5-15 minutes/module) consisting of daily training videos and *in vivo* on-demand exercises. Program features are designed to help users self-monitor their smoking habits, identify triggers for smoking, learn methods to become more aware of cravings and use mindfulness practices to ride them out. The program calculates and encourages a gradual taper over a 3-week period based on baseline cigarette use.

Participants in the control group used the National Cancer Institute's QuitGuide app (NCI) (https://smokefree.gov/tools-tips/apps/quitguide). NCI is based on the design and principles of Smokefree.gov, the most accessed smoking cessation website in the US. It includes strategies for quitting and health outcomes information.

*Expectancy evaluation*

Expectancy was assessed at baseline [4]. Post-treatment, participants were asked, "How likely are you to recommend this app to a friend?"

*Study Outcomes*

The primary outcome of this study was to demonstrate that app-based MT reliably decreased PCC reactivity to smoking cues.

*Functional MRI Task*

At each MRI visit, participants completed a previously-developed cue-reactivity task (Figure 1) [5,6]. To reduce variability related to cravings during the MRI task, participants smoked immediately prior to scanning. Participants were shown 60 smoking, 60 neutral, and 10 target images divided evenly across 5 scanning blocks lasting 5m18s each, for a total task time of 26.5 min. Images were presented for 4s each in a pseudorandom order. Participants were shown a fixation cross on a black screen during jittered inter-trial-intervals, which ranged from 6-14s (10s average). Smoking images included smoking-related content such as people smoking or holding cigarettes. Neutral images were matched for content. All images were novel in that no image shown on the pre-intervention visit was repeated during the second scan. Task instructions were to pay attention to all images, but to respond with a button-press any time they saw an image of an animal. Animals were used as target images to ensure participants stayed awake and attended to the task, but were not included in analyses. Between each of the 5 task scans, participants were asked whether they had fallen

asleep at any point during the scan and it was repeated if the participant reported falling asleep (*n* = 2, baseline).

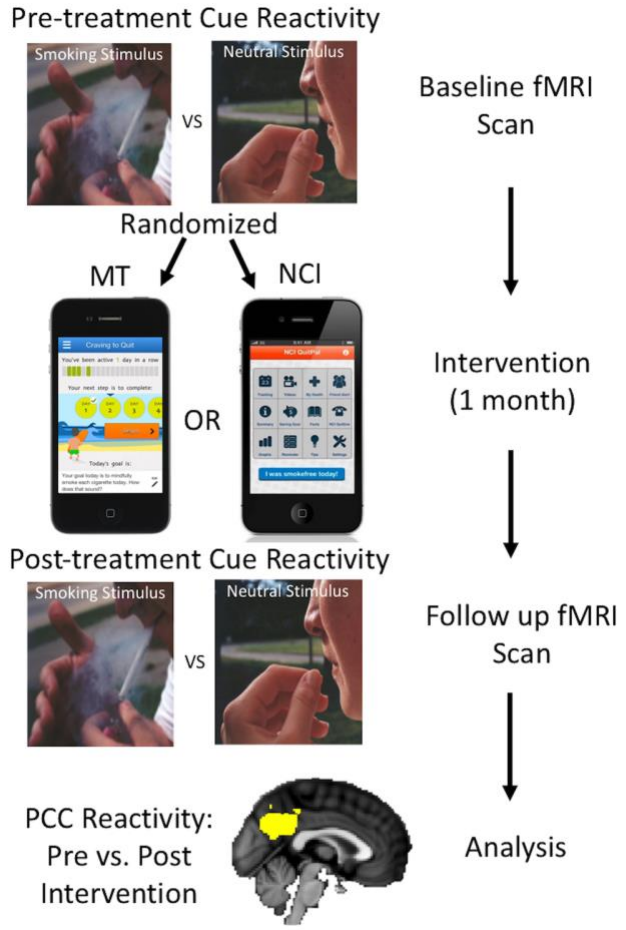


**Figure 1.** Study design. Yellow overlay on the anatomic brain image at the bottom represents the *a priori* defined PCC ROI derived from Janes et al (2015) for this analysis.

*Neuroimaging data collection*

Imaging data were collected on two Philips 3 Tesla MRI scanners. High-resolution anatomical MRI scans were acquired using the MPRAGE protocol with the following parameters: 181 (sagittal) slices, repetition time (TR)/echo time (TE): 7.0/3.2ms, shot interval: 3000ms, field of view (FOV) 240 x 240 x 181, matrix = 240x240; 1 mm isotropic

voxels. Cue-reactivity task scans were collected with the following parameters: 139 scans, 37 (transverse) slices; TR/TE: 2000/30ms, FOV 216 x 216 x 130, matrix = 80x80; 2.7x2.7x3.5mm voxels.

*fMRI preprocessing*

fMRI data analysis was conducted using tools from the fMRI of the Brain Software Library (FSL; www.fmrib. ox.ac.uk/fsl). The first five volumes for each run were removed to allow for signal stabilization. Functional data were pre-processed using the following: (1) motion correction with MCFLIRT, (2) brain extraction using BET, (3) slice timing correction, (4) spatial smoothing with a Gaussian kernel of full-width half-maximum 6 mm, and (5) high-pass temporal filter with Gaussian-weighted least-squares straight-line fitting with $\sigma$ =100s. A script was also used to detect and adjust for artifacts due to motion and intensity spiking prior to conducting preprocessing within FSL [7]. Participants' structural images were registered to the MNI152 2mm standard space template; corresponding functional datasets were transformed into standard space at $2mm^3$ resolution using the resulting registration transformation matrices.

*Cue-Reactivity Analysis*

First-level analysis was conducted on each of the participant's five cue-reactivity runs separately. First-level general linear model included three regressors, convolved with the gamma hemodynamic response function, corresponding to smoking, neutral, and target image presentation. Confound regressors based on rigid-body head-motion parameters were included to model motion effects. Consistent with our prior work [6,8],

another regressor was included that represented motion/intensity artifacts identified and removed prior to preprocessing. Contrasts between smoking and neutral image conditions were created for each run. First-level results were then combined across task scans using a second-level fixed effects analysis to obtain the average contrast-related brain reactivity for each participant. To determine the Group by Treatment interaction on PCC reactivity to smoking > neutral cues, a repeated measures ANOVA was conducted on beta-weights for smoking > neutral contrasts that were extracted from the PCC region-of-interest (ROI), which was based on an independent dataset evaluating the smoking > neutral contrast at the whole brain level (Figure 1, bottom) [6]. To examine between-group differences in pre- vs. post-treatment cue reactivity, the post-treatment PCC BOLD response for the smoking vs neutral contrast was subtracted from the baseline response. The groups were then compared directly on this measure using a t-test.

To confirm that the task activated the PCC at baseline, a group level voxel-wise analysis was conducted, restricting the analysis to the PCC. Cluster-level correction was applied using randomise, FSL's tool for nonparametric permutation inference, $z = 3.1$, $p < 0.05$.

*Study blinding*

Participants were blinded to group and team membership. Team members who randomized participants and performed scans did not perform study analyses. The

principal investigator and team members who conducted fMRI and statistical analysis were pseudo-blinded to group until all analyses were complete.

*Sample Size*

Our prior work with experienced meditators showed a percent signal change in PCC activity of -0.3 (SD = 0.2), while novices showed a percent signal change of 0.0 (SD = 0.2) [9], which yielded an effect size (ES) of 1.5. To be conservative we used an ES of 0.9 for power calculation; a sample size of 20 subjects/group provided 80% power to detect an ES of 0.9 with 2-sided 5% type I error using a 2-sample t-test.

*Correlation analysis*

The relationship between treatment-induced changes in PCC reactivity to smoking > neutral cues and the change in number of cigarettes smoked per day was evaluated using Spearman's correlation coefficient. Correlation comparison was performed using a standard z-test of Fisher's z-transformed correlations. Cigarette use change scores and change in PCC reactivity ($\Delta$) were calculated by subtracting baseline from post-treatment values. To examine the role of app modules in the change in smoking, a linear regression model was created for each group with change in smoking as the dependent variable and, as independent variables, $\Delta$ PCC, the number of modules completed, and the baseline number of cigarettes smoked. To determine whether effects were specific to the PCC, the medial prefrontal cortex (mPFC) and bilateral anterior insula (dAI) were evaluated. The mPFC (8mm sphere centered on x = -4, y = 54, z = 4) was chosen given that it typically co-activates with the PCC to smoking cues

and shows decreased activation in experienced meditators [9]. In contrast, the dAI ROI, which has been used in our prior work [6] does not show decreased activation in meditators, yet has been linked to nicotine dependence.

**References**


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