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RESEARCH ARTICLE

Testing the efficacy of real-time fMRI neurofeedback for training people who smoke daily to upregulate neural responses to nondrug rewards

Young In Chung[1] · Roisin White[2] · Charles F. Geier[3] · Stephen J. Johnston[4] · Joshua M. Smyth[5] · Mauricio R. Delgado[6] · Sherry A. McKee[7] · Stephen J. Wilson[1]

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Abstract

Although the use of nondrug rewards (e.g., money) to facilitate smoking cessation is widespread, recent research has found that such rewards may be least effective when people who smoke cigarettes are tempted to do so. Specifically, among people who smoke, the neural response to nondrug rewards appears blunted when access to cigarettes is anticipated, and this blunting is linked to a decrease in willingness to refrain from smoking to earn a monetary incentive. Accordingly, methods to enhance the value of nondrug rewards may be theoretically and clinically important. The current proof-of-concept study tested if real-time fMRI neurofeedback training augments the ability to upregulate responses in reward-related brain areas relative to a no-feedback control condition in people who smoke. Adults ($n = 44$, age range = 20-44) who reported smoking >5 cigarettes per day completed the study. Those in the intervention group ($n = 22$, 5 females) were trained to upregulate brain responses using feedback of ongoing striatal activity (i.e., a dynamic "thermometer" that reflected ongoing changes of fMRI signal intensity in the striatum) in a single neurofeedback session with three training runs. The control group ($n = 22$, 5 females) underwent a nearly identical procedure but received no neurofeedback. Those who received neurofeedback training demonstrated significantly greater increases in striatal BOLD activation while attempting to think about something rewarding compared to controls, but this effect was present only during the first training run. Future neurofeedback research with those who smoke should explore how to make neurofeedback training more effective for the self-regulation of reward-related brain activities.

Keywords fMRI · Neurofeedback · Smoking · Reward

Introduction

Smoking is the chief preventable cause of cardiovascular disease, lung and throat cancers, as well as many chronic respiratory illnesses, both in the United States and globally (Islami et al., 2015; Morris et al., 2015). Although rates are in decline, cigarette smoking is still prevalent; 14% of U.S. adults report that they currently smoked cigarettes in 2018 (Creamer et al., 2019). In addition, although 55% of people who smoked attempted to quit in the same year, fewer than one in 13 were successful. Accordingly, developing effective strategies for helping individuals to quit smoking and achieve long-term abstinence remains a top priority for public health.

One approach to facilitating smoking cessation that is rooted in well-established behavioral principles is contingency management, which involves using nondrug rewards

✉ Stephen J. Wilson
sjw42@psu.edu

1 Department of Psychology, The Pennsylvania State University, University Park, PA, USA

2 Novartis, Dublin, Ireland

3 Department of Human Development and Family Studies, The Pennsylvania State University, University Park, PA, USA

4 Department of Psychology, Swansea University, Swansea, Wales

5 Department of Biobehavioral Health, The Pennsylvania State University, University Park, PA, USA

6 Department of Psychology, Rutgers University, Newark, NJ, USA

7 Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

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(e.g., money) to reinforce abstinence from cigarettes (Stitzer & Petry, 2006). A recent, randomized, controlled trial examined four financial-incentive smoking cessation programs in more than 2,500 participants and found that the most effective incentive condition nearly tripled the quit rate relative to standard care (Halpern et al., 2015). Although these are highly encouraging findings, they are tempered by the observation that most of the participants who were provided with financial incentives did not abstain from cigarettes (73.9-85.5% across four programs) despite being offered a sizeable amount of money (up to $800 over a 6-month period) to do so. Several other incentive-based cessation studies have yielded a similar pattern of results (Baker et al., 2018; Etter & Schmid, 2016; Halpern et al., 2018; Volpp et al., 2009). Such findings highlight the promising but limited nature of using nondrug rewards to incentivize smoking cessation. Although this approach does significantly boost the odds of quitting and maintaining abstinence from cigarettes, even relatively large nondrug rewards are not sufficiently motivating to foster lasting behavior change for the majority of individuals who smoke cigarettes.

A key barrier to the effectiveness of reinforcement-based interventions for facilitating smoking cessation may be the deficits in reward functioning that are associated with cigarette smoking. A growing body of neuroimaging research have found that people who smoke have a dampened response to nondrug rewards in the striatum (primarily dorsal and ventral portions of the caudate nucleus and putamen), relative to people who do not smoke (Bühler et al., 2010; Jastreboff et al., 2015; Lessov-Schlaggar et al., 2013; Luo et al., 2011; Peters et al., 2011; Rose et al., 2012). Such differences may reflect preexisting deficiencies in dopaminergic motivational circuitry that increases the risk for cigarette use (Blum et al., 2000; Noble, 2000), neuroadaptations in brain reward systems that result from prolonged nicotine administration (Kalivas & Volkow, 2005; Koob et al., 2004; Perez et al., 2012), or some combination of the two. Regardless of their source, smoking-related differences linked to the striatum are likely to have significant implications for the use of contingency management and related strategies to aid smoking cessation, as the magnitude of the striatal response to reward varies systematically with how those rewards are appraised. Specifically, larger and/or more preferred rewards evoking stronger responses in the striatum than those that are smaller and/or less preferred (Delgado, 2007; Peters & Büchel, 2010).

Contextual factors, such as nicotine deprivation and cigarette availability, appear to play a part in further dampening striatal sensitivity to nondrug rewards in people who smoke (Pergadia et al., 2014; Wilson et al., 2008). For instance, abstaining from smoking for 24 hours, compared with smoking ad libitum, was associated with an attenuation of the response to monetary rewards in the striatum (i.e., caudate nucleus; Sweitzer et al., 2014), and between-person differences in the magnitude of this reduction predicted smoking cessation outcomes. Specifically, greater abstinence-induced decreases in the striatal response to rewards were associated with a significantly greater odds of lapsing during a subsequent 3-week quit attempt supported by contingency-management (Sweitzer et al., 2016). Acute nicotine abstinence also has been associated with reduced pleasure expectancies and responsiveness to financial incentive in people who smoke, independent of withdrawal symptoms (Powell et al., 2002). Regarding the effects of cigarette availability, individuals who were informed that they would have the opportunity to smoke soon demonstrated attenuated activation of the striatum (i.e., caudate nucleus) in response to winning money compared with those who were told that they would not be able to smoke until after a significant delay (Wilson et al., 2008). Moreover, the magnitude of striatal response to monetary rewards in those who were told that cigarettes would soon be available positively correlated with their willingness to further delay smoking to earn extra money (Wilson et al., 2014). These findings suggest that nondrug rewards may be even less effective at promoting abstinence when they are most required (i.e., during acute nicotine withdrawal and in moments when those who are quitting are tempted by the actual or anticipated availability of cigarettes).

Addressing decrements in the sensitivity to nondrug rewards that are related to smoking could help to improve cessation outcomes in people who are trying to quit. In particular, targeting striatal activity may be an innovative way to enhance the effectiveness of reward-based approaches to the treatment of smoking (and possibly drug addiction, more generally). Recent advances in neuroimaging capabilities have created novel methods for exploring this possibility. Specifically, real-time functional magnetic resonance imaging (fMRI) neurofeedback techniques, which allow the training of individuals to develop some degree of volitional control over activity in specific brain regions, may serve as an important new tool with which to help counteract nondrug reward-devaluation in people who smoke.

Although not focused on reward-related brain region, a small number of studies have investigated the efficacy of neurofeedback as a training tool for individuals who smoke cigarettes. The goal of most of this line of work has been to increase participants' ability to reduce cigarette craving using neurofeedback from the anterior cingulate cortex (ACC). These studies have shown that individuals who smoke are capable of significantly reducing BOLD signal in the ACC when presented with real-time fMRI neurofeedback and instructed to "reduce craving" compared with baseline and no-feedback control and that this reduction in ACC activation is associated with reduced self-reported craving (Hanlon et al., 2013; Hartwell et al., 2016; Li et al., 2013).

Given the lack of evidence-based interventions that directly target the dampening of sensitivity towards nondrug rewards in those who smoke, neurofeedback can be used to train people to upregulate activity in the striatum. Such training may provide a way to give them greater control over their motivational responses to nondrug rewards through the self-regulation of associated striatal responses (Dickerson, 2018). Specifically, individuals who smoke may be able to selectively apply the skills acquired through neurofeedback training to increase their sensitivity to nondrug rewards outside of the laboratory.

In support of this possibility, fMRI neurofeedback procedures for training individuals to increase activity in brain areas supporting reward-related processing and motivation have been used effectively in both community (Greer et al., 2014; Li et al., 2018;MacInnes et al., 2016 ; Sulzer et al., 2013) and clinical samples (e.g., cocaine dependence in Kirschner et al., 2018; alcohol dependence in Kirsch et al., 2016; major depressive disorder in Young et al., 2017). For instance, studies suggest that healthy individuals can learn to volitionally upregulate activity in the substantia nigra (Sulzer et al., 2013), ventral tegmental area (MacInnes et al., 2016; Sulzer et al., 2013), and nucleus accumbens (Greer et al., 2014; Li et al., 2018) when provided with real-time fMRI neurofeedback compared with those provided with control interventions. Collectively, this work highlights the potential of neurofeedback as a tool for teaching individuals strategies for enhancing reward-related brain responses, which they conceivably might then be able apply in a directed fashion in the context of specific stimuli (e.g., financial incentive).

The goal of the current proof-of-concept study was to determine whether people who smoke can learn to volitionally increase striatal activity when provided with neurofeedback targeting this region, relative to when no such feedback is provided, and whether this ability persists immediately after training in the absence of active feedback. Toward this end, people who smoke were randomly assigned to one of two groups. Those in the intervention group received real-time fMRI neurofeedback designed to train them to increase activity in the striatum using cognitive strategies (i.e., mental imagery) in the absence of explicit external rewards. Those in the control group also were asked to use cognitive strategies to increase their sense of reward and degree of motivation, but they did not receive any feedback about brain activity. Given the preliminary nature of this line of research, we elected to use a no-feedback control group to determine whether neurofeedback training improved the ability to self-regulate brain activity in reward-related areas compared with simple mental imagery instructions alone. We hypothesized that (a) compared with those in the control group, individuals in the intervention group would learn to significantly increase the blood oxygen level-dependent (BOLD) response in the striatum, (b) that this effect would increase across training runs, and (c) that the effect would be maintained following removal of active feedback. Finally, it is important to explore any widespread impact of neurofeedback training on the whole brain. We also examined potential changes outside of the striatum associated with neurofeedback training by conducting exploratory whole-brain analyses. We were particularly interested in investigating the possibility that learning to regulate striatial activation via neurofeedback training would produce wider changes in the activation of regions/networks supporting emotion regulation or positive emotion reappraisal, as this could have important therapeutic implications.

Materials and methods

Participants

Adults between the ages of 18 and 45 years who smoke cigarettes were recruited through flyers, newspaper, radio, and internet advertisements. Interested individuals completed a brief telephone interview to determine eligibility. In order to be eligible, individuals had to report that they smoked at least 6 cigarettes per day for the past 12 months and that they were not currently planning to quit smoking or actively pursuing any form of smoking cessation treatment. Individuals were excluded if they reported any of the following: current heavy use of alcohol, defined as four or more drinks per day for 10 days or more in the past 30 days; current heavy use of illicit substances, defined as illicit drug use for 10 days or more in the past 30 days; use of prescription medications that have been found to affect blood flow responses in the brain; major cardiovascular or respiratory disease during the past year; pregnancy; or any known risk from exposure to high-strength magnetic fields. Fifty-six individuals were enrolled in the study, with 48 completing all study procedures.[1] Of those completing the study, 44 yielded usable data (four were excluded because of data loss resulting from technical/equipment error). Following enrollment, participants were randomized into the neurofeedback or control group and scheduled for a baseline session. Figure 1 shows the consort figure of the study. All procedures were approved by the Pennsylvania State University Institutional Review Board. Individuals were paid US$215 in total for their participation.

[1] Six participants failed to schedule or show for the experimental session. One participant asked to be removed from the scanner due to claustrophobia. One participant indicated that they may have had metal in their eye during a final safety screening conducted just before being placed in the scanner (they denied having metal in their body during a prior screening).

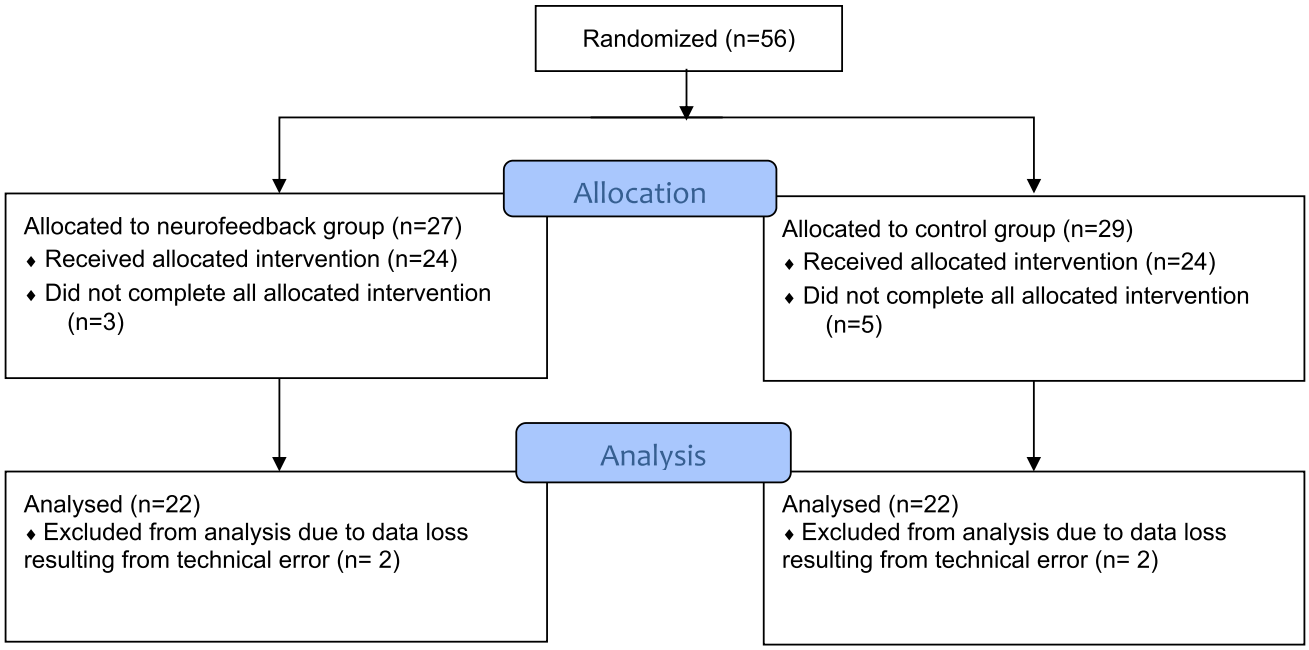

Fig. 1 Consort figure

Study design

Participants visited the lab for an initial baseline session. They then underwent a single fMRI neurofeedback training session on a separate day. The neurofeedback training session included a functional localizer paradigm, one pre-training run, three neurofeedback training runs, and one post-training run. Neurofeedback was not provided during the pre- and post-training runs. The two groups differed in that during the three training runs, the intervention group received feedback from a region of interest located in their striatum, whereas the control group followed the same instructions without receiving any neurofeedback. Participants were informed of the two study conditions in the consent form, which they reviewed at the start of the baseline screening session. The Consensus on the Reporting and Experimental Design of clinical and cognitive-behavioural Neurofeedback studies (CRED-nf) best practices checklist (Ros et al., 2020) is included in Supplementary Table 5.

Baseline session

During the initial baseline visit to the laboratory, participants provided an exhaled carbon monoxide (CO) sample, which was used to verify smoking status (≥9 parts per million; BreathCo, Vitalograph, Lenexa, Kansas). Participants were then administered a battery of computerized questionnaires and tasks, which are not a focus of the present study (see Supplementary Table 1 for full list). At the end of the baseline session, participants were scheduled for the neurofeedback training session.

Neurofeedback training session

Pre-scan assessments and instructions

Participants were instructed to smoke at their usual rate before the neurofeedback training session. At the beginning of the session, participants were asked the time at which they last smoked and how much they smoked on that occasion. Next, female participants self-administered a urine pregnancy test to ensure that they were not pregnant and showed the results to an experimenter. (No participants were screened out on the basis of this test.) All participants were then asked to smoke one of their own cigarettes to standardize time since last exposure to nicotine.

After smoking a cigarette, participants completed questionnaires measuring the following (in random order): symptoms of nicotine withdrawal (Minnesota Nicotine Withdrawal Scale [MNWS]; Hughes & Hatsukami, 1986); current levels of positive and negative affect (state version of the Positive and Negative Affect Schedule [PANAS]; Watson et al., 1988); smoking urge (Questionnaire of Smoking Urges-Brief [QSU-Brief]; Cox et al., 2001); and mental energy/fatigue (State Self-Control Capacity Scale [SSCCS]; Ciarocco et al., 2007). Next, using computerized visual analog scales (VAS; scored 0-100), participants were asked to rate the valence of their affective state (ranging from "unpleasant" to "pleasant"), their level of arousal

(ranging from "sleepy" to "aroused/activated"), and their urge to smoke (ranging from "no urge at all" to "strongest urge ever") (pre-scan VAS); VAS items were presented individually and in random order.

Participants were then shown a prerecorded presentation that included instructions regarding the strategies that they should use when attempting to increase activity in reward-related brain areas to fill up the thermometer during the scan session. These directions were modeled after those used by prior neurofeedback studies targeting striatal brain regions (Greer et al., 2014; Sulzer et al., 2013); e.g., "think about things that are most rewarding to you. For example, think about the money you just earned (from the Card-Guessing Task), your compliance bonus, and how you're going to spend that money, for example, on a nice meal or on a shopping trip." They were asked not to think about using the money to purchase cigarettes. Following the delivery of instructions, participants were placed into the scanner to complete the tasks described below.

Localizer task

Participants first completed an incentivized Card-Guessing Task adapted from Delgado et al. (2000). This task was chosen for two reasons. First, previous research has demonstrated that the task consistently and robustly activates reward-related brain regions, including the striatum (Delgado, 2007). Second, studies have shown that responses in the striatum (particularly the caudate nucleus) elicited by the task are linked to clinically meaningful outcomes in individuals who smoke (Sweitzer et al., 2014, 2016; Wilson et al., 2008, 2014), suggesting that such responses provide a useful target for intervention.

E-Prime software (Psychological Software Tools, Pittsburgh, PA) was used to control computerized stimulus presentation and the collection of responses and response latencies. During each trial of the task, participants guessed whether the value of a playing card presented on the screen would be higher or lower than 5. Participants were informed that they would receive $1 for correct guesses and lose $0.50 for incorrect guesses and that they were playing for real money to be received at the end of the session. Trials began with a choice-making period (2,000 ms), during which participants guessed via button press whether the value of a card would be higher or lower than 5. Next, a number from 1 to 9 (excluding 5) was presented (500 ms), followed by feedback informing participants whether or not their guess was correct (500 ms). Feedback for correct and incorrect guesses consisted of a green upward-pointing arrow (indicating a monetary gain) and a red downward-pointing arrow (indicating monetary loss), respectively. Unbeknownst to participants, card values were selected after their response on each trial. Trials were presented in a blocked format, with each block consisting of eight pseudo-randomly presented trials. Blocks were separated by 20-second rest periods. Participants performed two types of blocks: 1) high-gain blocks, which contained mostly gain trials (75% correct); and 2) high-loss blocks, which contained mostly loss trials (25% correct). The inclusion of a small number of incongruent trials in each block was designed to maintain participants' engagement and motivation to perform well. Participants were not aware of the specific outcome probabilities associated with each block. Participants were told that they would earn $0-40 of extra compensation (i.e., in addition to their base pay) based on their performance on the task. In actuality, outcomes were pseudorandomized (described as and appearing random, but actually predetermined), such that all participants earned $40. The localizer task took a total of 10 minutes to complete and was used to localize reward-related regions of interest (ROIs) for each participant, as detailed in Section, Localization of target ROIs. Following the task, participants provided VAS ratings of their craving, affect, and arousal (post-localizer task VAS).

Pre-training run

Next, participants performed a 6-minute "pre-training" run to assess baseline ability to upregulate reward-related brain activity in the absence of feedback. Throughout the run, subjects were presented with a static "thermometer" image comprised of blue and red bars via PsychoPy stimulus presentation software (version 1.76; Peirce, 2009). The thermometer was presented on a background that alternated between yellow and green every 20 seconds. During the yellow background, subjects were required to relax and rest with their eyes open. During the green backgrounds of the pre-training run, participants in both groups were asked to try to upregulate activity in brain reward areas as previously instructed (e.g., by thinking of something rewarding) without receiving neurofeedback (Fig. 2A). Participants were instructed that the thermometer would not change during pre- and post-training runs.

Training runs

After the pre-training run, participants completed three training runs, lasting 6 minutes each. During these runs, the intervention group was presented with a thermometer that changed dynamically to reflect the strength of fMRI signal from the target ROI identified in the localizer run, such that the thermometer "filled up" with red bars as brain activity in the target area increased and "emptied" to blue bars as activity in the target area decreased. The thermometer was presented on a background that alternated between yellow and green every 20 seconds. Participants in the intervention group were instructed to relax and rest with

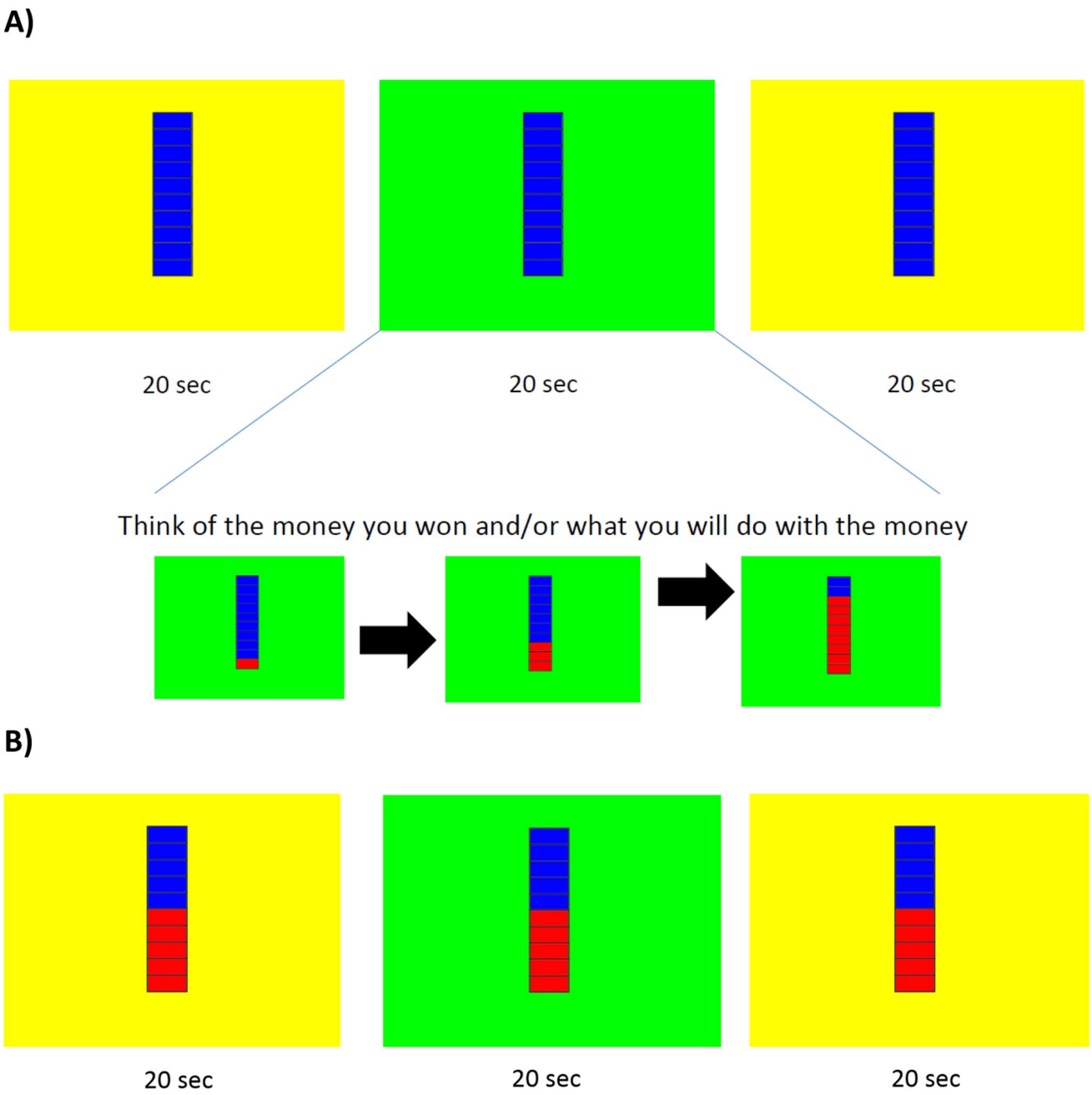

Fig. 2 (**A**) Depiction of the "thermometer" observed by participants in the active neurofeedback group during the training runs. When the background of the thermometer turned green, this signaled to participants that they should engage in cognitive strategies to increase BOLD response in reward-related brain regions, in turn increasing the level of the "thermometer." (**B**) Depiction of the static "thermometer" observed by participants in the no feedback control group during the training runs. When the background turned green, this signaled to participants that they should engage in cognitive strategies to increase their sense of reward and motivation

their eyes open when the yellow background was presented; they were required to attempt to increase the activation of the target ROI by increasing the height of the thermometer using mental imagery (as described above) when the green background was presented (Fig. 2A). The signal presented via the thermometer was expressed as percent signal change from the estimated baseline in the target ROI. Specifically, percent signal change was calculated by averaging fMRI signal in the target ROI over the three most recently acquired volumes, subtracting the average fMRI signal in the target ROI during the last two volumes of the preceding "rest" block, dividing this difference by the latter, and then multiplying the resulting value by 100. There were 10 gradations on the thermometer (each gradation represented a change

of 0.05%), and it was updated with the acquisition of each functional image (i.e., every 2 seconds). Participants in the intervention group were instructed to monitor the feedback signal and "tune" their strategy during successive blocks to determine the most successful approach for them, in accordance with procedures used in prior research (Johnston et al., 2010, 2011; Subramanian et al., 2011).

During the training runs, participants in the no-feedback control group were instructed to use the same types of cognitive strategies as above (e.g., thinking of rewarding things) to increase their sense of reward and degree of motivation but were not provided with feedback about brain activity. Like the intervention group, they were presented with a thermometer on a background that alternated between yellow (rest) and green (upregulate). However, the height of the thermometer was fixed (half full of red bars) throughout the run.

Post-training run

Following the three training runs, participants in both the intervention and control groups performed a 6-minute "post-training" run, where they were again asked to try to upregulate activity in brain reward areas using cognitive strategies (e.g., thinking of something rewarding) without receiving neurofeedback (i.e., the thermometer remained half-full throughout the run for each group). At the conclusion of the post-training run, participants provided VAS ratings of their craving, affect, and arousal (post-training run VAS).

Anatomical scan and additional task

Next, participants completed a 6-minute structural scan, during which participants viewed a computer-generated video presentation designed to minimize head movement (Vanderwal et al., 2015) and then provided VAS ratings of their craving, affect, and arousal (post-structural scan VAS). Finally, participants completed a modified version of the Card-Guessing Task, consisting of one 10-minute run during which both groups attempted to apply strategies used during the training runs while performing the task. Data from this task was not the focus of the current study and will be reported elsewhere. Participants completed a final VAS assessment of craving, affect, and arousal immediately before being removed from the scanner (post-scanning VAS).

Post-scan assessments

Following removal from the scanner, participants completed the state version of the PANAS, the QSU-Brief, the MNWS, and the SSCCS. Finally, participants in both groups were asked to describe the cognitive strategies they used while in the scanner and to identify which approaches they felt were most effective. Most participants reported that they tried thinking about different rewards and identified more than one effective strategy. Of the 44 participants, 16 participants reported that concentrating on the social rewards (e.g., partner's smiles) was the most effective. Fifteen participants reported that thinking about the money itself or buying expensive things/experiences was effective. Other successful strategies included thinking about food (6 participants), achieving personal goals (7 participants), and sexual imagery (3 participants). Five participants reported that none of their mental strategies worked or that they used other relaxation strategies.

Imaging data acquisition

The study was conducted at the Penn State Social, Life, & Engineering Sciences Imaging Center using a 3-Tesla Siemens Magnetom Prisma scanner equipped with a 20-channel head coil. For each participant, a high-resolution, three-dimensional, T1-weighted, anatomical image was obtained by using a magnetization-prepared, rapid acquisition gradient echo pulse sequence (repetition time = 2,300 ms, echo time = 2.28 ms, field of view = 256 mm, flip angle = 9°, 1.0 x 1.0- x 1.0-mm voxels, 192 sagittal slices). Functional images were collected using a one-shot echo-planar imaging pulse sequence (repetition time = 2,000 ms, echo time = 25 ms, field of view = 192 mm, flip angle = 80°, 3.0- x 3.0- x 3.0-mm voxels, 35 axial slices acquired parallel to the anterior commissure-posterior commissure plane).

Localization of target ROIs

As indicated earlier, the Card-Guessing Task was used to localize reward-related ROIs for each participant. This was performed during the scan session for those in the neurofeedback condition and during offline analysis for those in the control condition using Turbo BrainVoyager software (version 3.2; Weiskopf et al., 2003). Briefly, Turbo-BrainVoyager rapidly preprocessed and analyzed incoming fMRI data by way of incremental general linear models (GLMs), which included a predictor for each type of task block condition (high gain and high loss) convolved with a hemodynamic reference function. The first ten volumes of the sequence were discarded to avoid T1 saturation effects. Data were corrected for motion (both translational and rotational) and spatially smoothed (4-mm FWHM Gaussian kernel) online. Target ROIs within the striatum were isolated using a contrast of high reward > high loss, enabling the localization of brain (i.e., striatal) areas that were maximally responsive to nondrug (monetary) rewards relative to losses within individuals. Signal from the subject-specific voxels identified with the localizer task was used to calculate the feedback presented to participants in the neurofeedback group during the subsequent training runs, as detailed above (see Section, Training runs).

Preprocessing for offline analysis

Processing of the fMRI data was performed by using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl; version 5.0.9). Registration to high-resolution structural and standard space (2-mm resolution Montreal Neurological Institute [MNI] template) images was performed by using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Registration from high-resolution structural to standard space was then further refined by using FNIRT nonlinear registration (Andersson et al., 2007a, 2007b). The following prestatistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002); slice-timing correction using Fourier-space time-series phase-shifting; nonbrain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 45.0 s).

Analysis plan

ROI analysis

Multilevel modeling was used to assess the effect of the neurofeedback intervention on the ability to increase BOLD activation in individually identified striatal ROIs (quantified as percent signal change extracted using Featquery), following an approach utilized by prior fMRI neurofeedback research (Hartwell et al., 2016). This approach is conceptually comparable to a repeated-measures ANOVA but has several advantages; primarily, it uses maximum likelihood estimation to handle missing data, while an ANOVA uses listwise deletion. Fixed effects for group (intervention vs. control), time (training runs 1 through 3) and a group x time interaction were estimated. Baseline ability to increase striatal BOLD activation during the pre-training run was included as a covariate. Participants were specified as a random factor to control for the influence of different mean scores (intercepts) for each individual (i.e., a random intercept model; Pinheiro & Bates, 2000). The model was fitted using the nlme package within the R software environment. We hypothesized that groups would emerge as a significant predictor of ROI activation during training runs. Specifically, we hypothesized that individuals in the intervention group would demonstrate significantly larger increases in activation during the training runs than controls. We further hypothesized that there would be a significant group by time interaction, such that the intervention group would display a larger increase in the ability to upregulate striatal activation in later training runs than the control group. T-tests were conducted to investigate significant differences associated with interaction effects (i.e., to compare group differences for each run).

A multilevel model was also conducted using the pre- and post-training run data to investigate whether the two groups differed in ability to upregulate striatal activation following the training protocol. Due to time constraints, one participant in the control group did not complete the post-training run; all available data were included in the model. Similar to above, we predicted that there would be a significant group by time interaction, with individuals in the intervention group exhibiting a significantly larger increase in ROI activation from the pre-training run to the post-training than those in the control group. Significance of effects was evaluated at $\alpha = 0.05$.

Exploratory whole-brain analysis

Two exploratory whole-brain analyses were conducted at the group level using 3dLME (Chen et al., 2013) from the Analysis of Functional NeuroImages (AFNI; version 17.3.03) suite (Cox, 1996). The first model included data from the training runs. As before, fixed effects for group (intervention vs. control) and time (training runs 1 through 3) as well as their interaction were estimated along with random intercepts per participant, and pre-training maps were included as a voxel-wise covariate. A second model assessed the pre- and post-training data and included fixed effects for group, time (pre-training run, post-training run), and a group x time interaction (with post-training run data missing for one participant, as noted above). The threshold for each model was determined with the AFNI program 3dClustSim using the following parameters: a cluster-forming threshold of $p = 0.001$; 10,000 Monte Carlo simulations; and average smoothness of the residuals across participants, as estimated using the spatial autocorrelation function implemented in the AFNI program 3dFWHMx (Cox et al., 2017). Using this approach, it was determined that combining a cluster-forming threshold of $p = 0.001$ with minimum cluster sizes of 66 voxels (528 mm^3) and 68 voxels (544 mm^3) would achieve a family-wise error corrected $p < 0.05$ at the cluster level for the first and second models, respectively; only clusters meeting these criteria were considered significant. Whole-brain analyses were not designed to test specific hypotheses and are included primarily to facilitate future research.

Analysis of self-report data

Changes in subjective ratings of affective valence, level of arousal, and urge/craving to smoke taken throughout the scan were similarly assessed using a mixed-effects framework, controlling for pre-scan (baseline) ratings. In each case, fixed effects for group (intervention vs. control), time (post-localizer task VAS, post-training run VAS, post-structural scan VAS, post-scanning VAS), and a group x time interaction were estimated. For each model, pre-scan VAS (baseline) ratings were included as a covariate, and participants were specified as a random factor to control for the influence of different mean

Table 1 Sample characteristics

	Full sample (n = 44)	Neurofeedback group (n = 22)	Control group (n = 22)
Mean (SD) age in years	26.7 (7.5)	26.2 (7.6)	27.2 (7.6)
Number male/female	34/10	17/5	17/5
Mean (SD) cigarettes/day	14.6 (6.7)	13.7 (6.4)	15.5 (7.1)
Mean (SD) years of regular smoking	9.7 (7.8)	8.8 (7.5)	10.6 (8.2)
Mean (SD) FTCD score	3.9 (2)	4.2 (1.9)	3.7 (2.1)
Education level (percentages)			
< High school graduate	2.3	4.5	0
High school graduate or GED	31.8	27.3	36.4
Some college or technical school	50	59.1	40.9
Four-year college graduate	16	9.1	22.7
Employment status (percentages)			
Unemployed	54.5	54.5	54.5
Employed part-time	22.7	18.2	27.3
Employed full-time	22.7	27.3	18.2

scores (intercepts) for each individual. Mixed-effects models were also conducted using the pre- and post-scan questionnaire data measuring symptoms of nicotine withdrawal (MNWS), state positive and negative affect (state version of the PANAS), urge to smoke (QSU-Brief), and mental energy/fatigue (SSCCS). Two participants (both in the intervention group) failed to complete the QSU-Brief and SSCCS before the scan, and one participant (control group) failed to complete the QSU-Brief, SSCCS, state version of the PANAS, and MNWS after the scan. In addition, the following VAS ratings were missing due to technical error and/or time constraints: pre-scan ratings for two participants (both in intervention group); post-training runs ratings for two participants (both in the control group); post-structural scan ratings for one participant (control group); and post-scanning ratings for seven participants (three in intervention group and four in control group). Analyses of subjective ratings included all available data.

Results

Sample characteristics

Table 1 reports select demographic and smoking-related characteristics for the full sample and for each group. The self-identified racial and ethnic composition of the usable sample was as follows: 65.9% Caucasian; 20.5% Asian; 9.1% multiracial; 2.3% black or African American; 2.3% American Indian or Alaskan Native; 95.5% of participants identified as not Hispanic or Latino; and 4.5% identified as Hispanic or Latino. Groups were similar in terms of age, distribution of gender or self-identified race/ethnicity, cigarettes/day, years smoking, nicotine dependence (as assessed using the Fagerström Test for Cigarette Dependence [FTCD]; Fagerström, 2012), years of education, and employment status (p values > 0.3).

Localization of target ROIs

Target ROIs localized to the striatum (primarily the caudate nucleus) were successfully identified for all participants using the Card-Guessing Task. The average location and size of target ROIs was similar across groups. Regarding the former, the mean (*SD*) MNI coordinates for the center of gravity of the target ROIs were x = 2.5 (8.5), y = 11.1 (6.2), z = 6.7 (3.6) for the neurofeedback group and x = 1.9 (4.1), y = 11.5 (3.9), z = 4.3 (4.9) for the control group. Figure 3 shows the center of gravity of the individually identified ROIs in MNI space for each group (coordinates for each participant are presented in Supplemental Table 2). The mean (*SD*) volume of target ROIs was 5,734.5 (4,374.3) mm^3 for the neurofeedback group and 4,236.7 (3,917.7) mm^3 for the control group; this difference was not significant ($t(42) = 1.20$, $p > 0.2$).

ROI analysis

Training runs

Results of the linear mixed-effects model predicting activation in striatal ROIs during the training runs are presented in Table 2. There was a significant positive association between activation of striatal ROIs during the pre-training and training runs ($\beta = 0.50$, $p < 0.001$). Group also was significantly associated with activation of striatal ROIs during the training runs

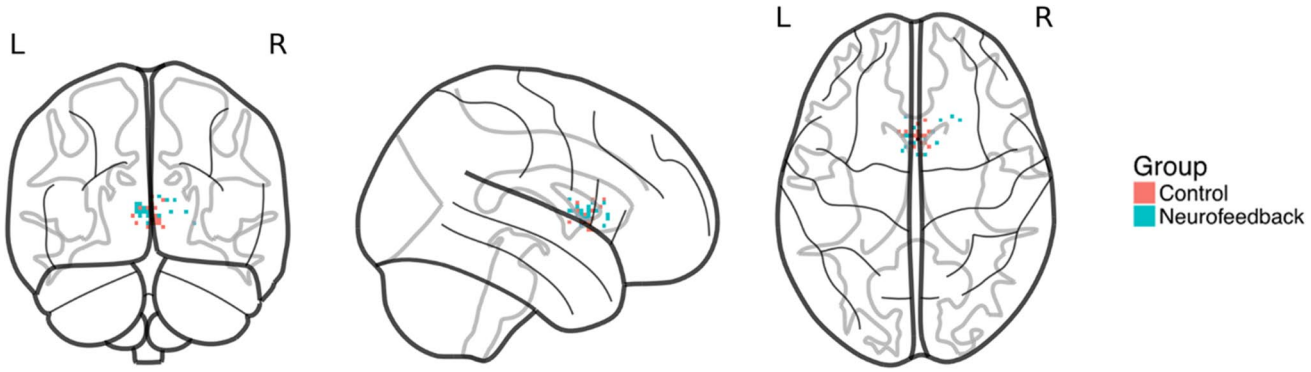

Fig. 3 Glass brain showing the center of gravity of the region of interest for each participant in the neurofeedback and control groups in Montreal Neurological Institute space

($\beta = 0.24$, $p = 0.02$), such that the intervention group demonstrated significantly larger increases in activation during the training runs compared to the control group. However, there was also a trend-level group x time interaction ($\beta = -0.07$, $p = 0.06$), suggesting that the main effect of group was not distributed evenly across training runs. As shown in Fig. 4, those in the intervention group demonstrated significantly greater activation of striatal ROIs during training run 1 only ($t(42) = 2.19$, $p = 0.03$); there were no significant differences in activation between the groups during training runs 2 and 3 ($t(42) = 1.20$, $p = 0.24$ and $t(42) = 0.58$, $p = 0.57$, respectively).

Follow-up *t*-tests revealed that the two groups did not differ in the activation of striatal ROIs during pre-training baseline ($t(42) = -0.60$, $p = 0.55$). We tested the significance of the change of activation from pre-training baseline to training run 1 for each group. There was a nonsignificant increase in activation from baseline to run 1 for the intervention group ($t(21) = 1.41$, $p = 0.17$), whereas there was a nonsignificant decrease of activation from baseline to run 1 for the control group ($t(21) = 1.76$, $p = 0.09$).

Pre-/post-training runs

Analysis of data from the pre- and post-training runs indicated that activation of striatal ROIs was not significantly associated with group ($\beta = -0.07$, $p = 0.64$), time (pre- versus post-training; $\beta = 0.04$, $p = 0.55$), or the group x time interaction ($\beta = 0.02$, $p = 0.84$).

Whole-brain analyses

Training runs

A main effect of time was observed in the right angular gyrus (MNI coordinates for local maximum: x = 54, y = −54, z = 12; size = 158 voxels/1,264 mm^3); activation was lower in this region during the first training run relative to the second and third training runs, while activation was similar for the latter two runs. Both a main effect of group and a group x time interaction were observed in the right inferior frontal gyrus (rIFG) extending to portions of the anterior insula, with significant spatial overlap in these effects. Figure 5A depicts the location of the main effect (x = 40, y = 20, z = 6, 116 voxels/928 mm^3) and interaction (x = 38, y = 22, z = 8; 87 voxels/696 mm^3). Figure 5B presents mean activation across training runs (adjusted for activation during the pre-training run) for both groups in the region exhibiting an interaction effect. As shown, those in the intervention group demonstrated significantly greater activation than controls during training run 1, with no significant differences in activation between groups for training runs 2 and 3.

Pre-/post-training runs

There was a significant main effect of group in the posterior cingulate gyrus (x = −6, y = −56, z = 12; size = 330

Table 2 Linear mixed-effects model predicting activation (percent signal change) in ROIs during the training runs

Fixed effects	*Estimate*	*Standard Error*
Intercept (γ_{00})	−0.07	0.07
Pre-training (γ_{01})	0.50*	0.12
NFBK group (γ_{02})	0.24*	0.10
Time (γ_{10})	0.04	0.03
NFBK group * Time (γ_{11})	−0.07	0.04
Random effects	*Estimate*	*95% CI*
Intercept (σ^2_{w0})	0.18*	0.14–0.24
Fit indices		
AIC	15.74	
BIC	35.64	

AIC = Akaike information criteria; BIC = Bayesian information criteria; CI = confidence intervals. **indicates* $p < 0.05$

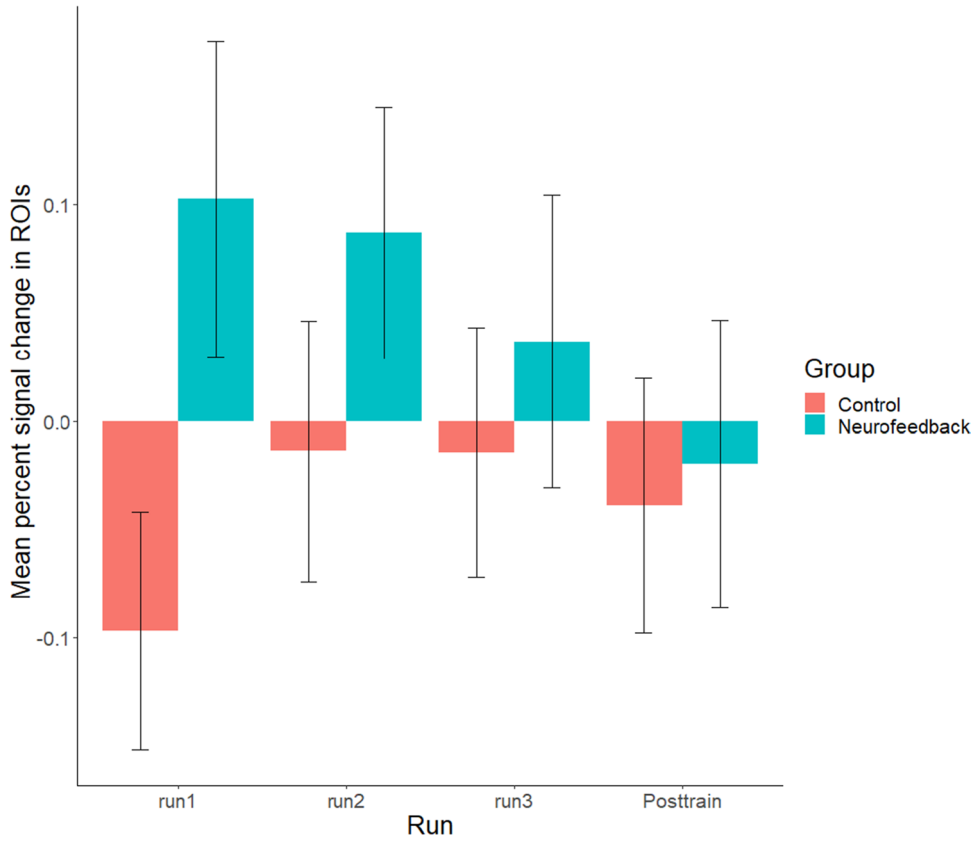

Fig. 4 Barplot showing mean activation between the neurofeedback and control groups, controlling for the activation during pre-training run

voxels/2,640 mm^3), with the intervention group having lower activation in this region than the control group. No regions exhibited a significant main effect of time or group x time interaction.

Subjective ratings analysis

Results from the linear-mixed effects models predicting change in affective valence, level of arousal, and urge/craving to smoke during the scan (VAS ratings) indicated no significant main effects of group or group x time interactions on any of the three outcomes (Table 3). However, significant main effects of time were found predicting affective valence ($\beta = -5.14$, $p < 0.001$) and urge/craving to smoke ($\beta = 5.21$, $p < 0.001$), such that valence ratings decreased (i.e., became less positive) and craving increased over the course of the experimental session. Similarly, models predicting pre- to post-scan changes in response to questionnaires assessing symptoms of nicotine withdrawal (MNWS), state positive and negative affect (state version of the PANAS), smoking urge (QSU-Brief), and mental energy/fatigue (SSCCS) found no significant main effects of group or group x time. Main effects of time were found in models predicting symptoms of nicotine withdrawal ($\beta = 7.41$, $p < 0.001$), smoking urge ($\beta = 9.68$, $p = 0.02$), and mental energy/fatigue ($\beta = -26.05$, $p = 0.01$), indicating that, regardless of group, participants demonstrated greater levels of nicotine withdrawal symptomatology and urge to smoke, as well as lower levels of mental energy, following the scan compared with the pre-scan assessment. Mean VAS ratings and scores on experimental session questionnaires are presented in Supplemental Tables 3 and 4, respectively.

Discussion

The present proof-of-concept study investigated whether real-time fMRI neurofeedback techniques could be used to train people who smoke cigarettes on a daily basis to volitionally increase striatal activity. Results indicate that overall, participants who received neurofeedback showed greater striatal activation during up-regulation blocks than the control group during the three training runs. Specifically, during the first training run, those in the neurofeedback group exhibited significantly greater activation (quantified as percent signal change) relative to the control group. However, the effect of neurofeedback attenuated and did not maintain statistical divergence from the control condition during training run 2 and 3. Across the three training runs, striatal

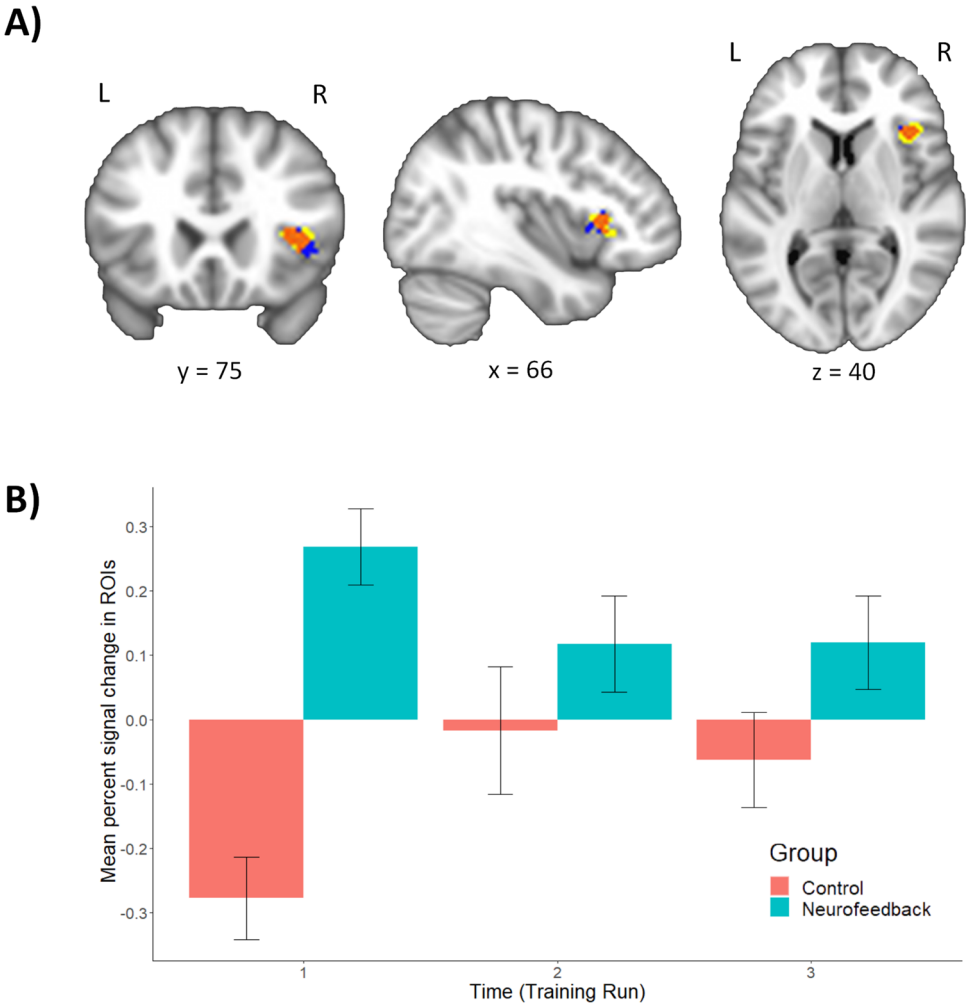

Fig. 5 (**A**) Brain figure showing overlapping areas of the right inferior frontal gyrus and anterior insula exhibiting a main of group and a group x time interaction. Areas exhibiting only a main effect of group or an interaction effect are depicted in yellow and blue, respectively, whereas overlapping areas are depicted in orange. (**B**) Barplot showing mean differences in activation between the neurofeedback and control groups across the three training runs in the region exhibiting a significant group x time interaction

Table 3 Mixed-effects models predicting subjective ratings of affective valence, arousal, and craving (VAS ratings)

	Affective valence	Arousal	Craving
Fixed effects	*Estimate (SE)*		
Intercept (γ_{00})	58.29* (13.71)	45.78* (9.74)	15.24* (6.15)
Pre-scan baseline (γ_{01})	0.20 (0.16)	0.26* (0.12)	0.57* (0.11)
NFBK group (γ_{02})	0.06 (8.22)	5.16 (8.47)	10.60 (7.24)
Time (γ_{10})	−5.14* (1.30)	−2.89 (1.53)	5.21* (1.03)
NFBK group * Time (γ_{11})	2.83 (1.86)	−1.32 (2.19)	−0.39 (1.48)
Random effects	*Estimate (95% CI)*		
Intercept (σ^2_{w0})	18.16* (13.83–23.85)	15.09* (10.88–20.91)	17.68* (13.72–22.78)

**indicates $p < 0.05$*

activation decreased with time in the neurofeedback group. In contrast, striatal activation did not change significantly over time during the training runs for the control group. Furthermore, the neurofeedback and control groups did not differ in striatal activation during the post-training run, indicating a lack of transfer effect following the removal of neurofeedback. Taken together, the findings did not provide support for our hypothesis that neurofeedback training would significantly enhance the ability to upregulate reward-related brain activation in people who smoke.

Although the presentation of neurofeedback was associated with an initial increase in striatal activation relative to the control condition, we cannot conclude that this increase in activation was an effect of a volitional control of the striatum. The time-limited effect of neurofeedback may have been driven by effects other than those specifically targeted by neurofeedback (Ros et al., 2020). That is, independent from the act of volitionally controlling the target region, other factors, such as the novelty of the neurofeedback information, could have served as a reward, driving the initial increase of striatal activation for individuals who received neurofeedback. This could help to explain why the neurofeedback group displayed a nonsignificant increase in striatal activation during the first training run relative to their pre-training baseline, whereas the control group showed a nonsignificant decrease in striatal activation across this period. Similarly, various factors may have influenced the subsequent attenuation of the group difference across the second and third training runs, such as participants' habituation to the novelty of the neurotechnological information or a greater increase in fatigue over time in the intervention group compared with the control group. It is difficult to rule out these and related possibilities without the inclusion of additional control groups (e.g., sham control) to account for the intrinsically rewarding effect of receiving neurofeedback.

Our results are inconsistent with previous findings that fMRI-based neurofeedback targeting reward-related regions is effective when used to train people who are healthy (Greer et al., 2014; Kirsch et al., 2016; Li et al., 2018; MacInnes et al., 2016). This inconsistency highlights important points about conducting neurofeedback training with different populations. Given prior evidence suggesting that chronic exposure to nicotine is associated with attenuated striatal response to natural rewards (Rose et al., 2012), people who smoke may have greater difficultly learning to self-regulate activity in reward-related regions via neurofeedback than those who do not smoke. A growing body of neurofeedback studies suggests that brain regions involved in reward processing (including the striatum) play a key role in the acquisition of self-regulatory skills for brain activity during neurofeedback training (Sitaram et al., 2017). For instance, a recent study demonstrated that better neurofeedback performance was associated with greater activation within the striatum across different mental tasks (Skottnik et al., 2019). This may imply that people with chronic exposure to nicotine have altered functioning in the very region that is involved in learning and benefiting from neurofeedback.

Even so, there is some evidence that people who smoke can benefit from neurofeedback training, especially related to reducing cue-reactive craving (Canterberry et al., 2013; Hanlon et al., 2013; Hartwell et al., 2016; Li et al., 2013). However, a recent review paper highlighted the limitations of previous neurofeedback studies on smoking, in that most were underpowered and lacked an adequate control condition (Pandria et al., 2020). It will be important for future research examining the clinical utility of neurofeedback for the treatment of smoking and other substance use problems to address such limitations (e.g., by including larger samples and adopting designs that increase internal validity), as well as explore ways to tailor neurofeedback training to the unique needs of the targeted population. As shown in the present study, participants in both groups experienced increasingly more negative affect, more fatigue, and stronger urge to smoke over the course of the training, which could have interfered with learning. To make neurofeedback trainings more efficient and mentally less draining, complementary strategies designed to enhance reward sensitivity may serve as a particularly useful addition for people who smoke and other populations characterized by reward-related deficiencies. A recent review article highlighted systematic mental imagery training, which has proven to be an effective treatment for various psychological disorders (including depression, anxiety disorders, and addiction), as a tool for enhancing the potency of neurofeedback interventions (Skottnik & Linden, 2019). Moreover, recent work has shown that formal mental imagery training can be used to enhance the subjective experience of reward. For example, studies testing a relatively new intervention called Mindfulness-Oriented Recovery Enhancement (MORE) that incorporates mental imagery have shown that it is effective for increasing both reward-related activation of the ventral striatum (i.e., ventral portions of the caudate nucleus and putamen) and positive affect (Froeliger et al., 2017; Garland, 2016). Future research examining the utility of combining interventions such as MORE with neurofeedback to increase reward sensitivity in people who smoke would be valuable.

Furthermore, a closer look at previous neurofeedback studies targeting the mesolimbic dopaminergic system reveals methodological variability that makes it challenging to generalize and reproduce findings. One issue is that the approaches used to evaluate regulation success differ widely across studies. For instance, improved activation during training runs relative to the pre-training run (Sulzer et al., 2013), significant within-person difference in peak activation during feedback versus no-feedback blocks (Greer

et al., 2014), linear increase in activation across the training runs (Li et al., 2018), greater sustained activation during regulation trials relative to a control group (MacInnes et al., 2016), and greater sustained activation during post-training relative to pre-training and to control group (MacInnes et al., 2016), have all been cited as evidence that neurofeedback helps improve participants' ability to control reward-related brain activity. Similarly, prior studies have used different baselines to calculate feedback. A consensus regarding analytic approaches and reporting standards will help elucidate the effectiveness of neurofeedback targeting brain reward regions in both clinical and nonclinical populations (Fede et al., 2020; Paret et al., 2019; Ros et al., 2020).

It is important to note several limitations of the current study. As discussed earlier, we included a control group that practiced similar mental strategy but without feedback. Because neurofeedback research with clinical population is still in an exploratory stage, we hoped to establish whether neurofeedback training improved the ability to self-regulate brain activity in reward-related areas compared with simple mental imagery instructions alone as an initial step in a broader line of research. Although we believe that the approach adopted in the current study is a reasonable first step (Sorger et al., 2019), it does not allow for the effect of volitional control of the striatum to be separated from the rewarding effect of the neurofeedback information. This issue could be addressed using other control conditions, such as sham feedback from a non-target brain region or from a matched participant assigned to the neurofeedback group. However, there is some evidence that such controls can produce frustration as well as an incongruence between the feedback and participants' internal representation (Hartwell et al., 2016; Sorger et al., 2019), both of which could affect striatal activity. Another limitation of the current study is that it consisted of only one session of neurofeedback training. Because we instructed the participants to test different strategies to increase the neurofeedback thermometer instead of relying on one mental imagery, the striatal activation may not have increased in a linear way across the three training runs. Assessing longer-term change (e.g., over multiple scan sessions), which might provide more of an opportunity to practice effective strategies identified through trial and error, may better capture the effects of learning. In a multivisit neurofeedback study involving the regulation of craving-related activity in people who smoke, Hartwell et al. (2016) found that the performance improved incrementally across three visits in the neurofeedback group. Future research could investigate the ability to upregulate brain responses to nondrug rewards across multiple sessions to ascertain the optimal amount of training. Finally, the inclusion of people who smoke who were not interested in quitting as participants in the current study and the fact that participants were trained in a state of minimal cigarette deprivation limit generalizability to clinical contexts. Research addressing these issues by directly testing the extent to which reward-focused neurofeedback facilitates cessation in people who want to quit smoking would be valuable, as would work that examines the effectiveness of neurofeedback targeting reward processing at different points during a quit attempt (e.g., by examining neurofeedback as a relapse prevention tool after cessation has been initiated).

In summary, we found a significant difference in the ability to increase striatal activation between people who smoke who were provided with neurofeedback compared to those who were not, but this difference was short lived and may not specifically reflect learning effects. Taken together, the results from the current study suggest that simply instructing people who smoke to use reward-related mental imagery while providing them with neurofeedback may not be sufficient to teach them to self-regulate activity in the striatum. Although this may appear inconsistent with previous neurofeedback studies targeting brain reward areas, closer inspection of these studies highlights key methodological inconsistencies that make it difficult to draw strong conclusions from prior work. In addition to resolving such inconsistencies, future research focused on people who smoke and other clinical populations characterized by reduced sensitivity to rewards (e.g., people addicted to substances other than nicotine, people with depressive disorders) should examine whether the effectiveness of neurofeedback can be increased by lengthening the duration of the intervention (e.g., using multiple sessions) and/or by combining it with promising treatment techniques such as comprehensive mental imagery training. Doing so would help to identify boundary conditions regarding the potential utility of neurofeedback targeting reward functioning in people who smoke and other clinical populations.

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

Code availability The code that supports the findings of this study is available from the corresponding author upon reasonable request.

Declaration

Ethics approval All procedures were approved by the Pennsylvania State University Institutional Review Board. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Conflicts of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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