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Reduction of cue-induced craving through realtime neurofeedback in nicotine users: The role of region of interest selection and multiple visits

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Abstract

This multi-visit, real-time functional magnetic resonance imaging feedback study demonstrates that treatment-seeking smokers can effectively modulate their behavioral and brain responses to smoking cues. They are more effective at decreasing activity in functionally defined regions involved in “craving” (e.g. ventral anterior cingulate cortex (vACC)) rather than increasing activity in regions involved in “resisting” (e.g. dorsal medial prefrontal cortex (dmPFC)).

Keywords

Addiction; Prefrontal cortex; Cingulate

1. Introduction

Loss of control over drug-taking is a hallmark of addiction (Baler and Volkow, 2006). Substance-dependent individuals often have a diminished sense of agency over their actions (Bunch and Schneider, 1991; Zeiner et al., 1985), and are highly responsive to immediate rewards (Bickel and Yi, 2008; Potenza, 2007). Smokers with a higher sense of agency over their actions, however, have significantly better outcomes during smoking cessation attempts (Gregor et al., 2008; McKenna and Higgins, 1997; Rosenbaum and Argon, 1979).

Real-time functional magnetic resonance imaging (rtfMRI) is a relatively new neuroimaging technique that may enhance individuals' sense of agency by providing them with ongoing feedback about their neural response to a certain cue and instructing them to increase or attenuate that response. This technique has been explored for pain (deCharms et al., 2005), anxiety (Caria et al., 2010; Johnson et al., 2012), and recently addiction (Li et al., 2012). The optimal spatial and temporal parameters for rtfMRI experiments, however, are unknown and

likely unique to each disease state. The primary goal of this multi-visit rtfMRI study was to determine whether smokers receive maximal benefit from trying to *decrease activity in a brain region activated by smoking cues* or *increase activity in a brain region activated when trying to resist the urge to smoke*.

2. Methods

Participants were recruited through advertisements in local print and broadcast media. Interested individuals contacted us by phone wherein they were given a brief questionnaire (prescreening). Participants that met initial criteria were invited in for a screening visit ($n = 21$) wherein they provided informed consent and were asked a series of questions about their medical and social history including current and past drug and alcohol use. Given the limited time available for a thorough neuropsychiatric evaluation in these nicotine smokers, lifetime psychopathology was assessed with the Mini-International Neuropsychiatric Interview. Fifteen right-handed, treatment-seeking, nicotine-dependent smokers (10 cigarettes/day, 21–45 years old) were recruited through local resources. Exclusion criteria were as follows: current nicotine replacement therapy, bupropion, varenicline, psychoactive medications, past neurological illness, Axis-I psychiatric disorder, hypertension, cardiac disease, diabetes, pregnancy, and history of non-nicotine substance dependence. All procedures were approved by the MUSC Institutional Review Board.

Eligible participants were scheduled to attend three rtfMRI scanning visits (inter-visit interval = 7–10 days). During each visit participants were exposed to four runs of an established nicotine cue-induced craving paradigm (blocks of smoking-related images, neutral-images, and rest) (Hartwell et al., 2011; Geier et al., 2000). During Region of Interest (ROI) Isolation runs (Runs 1 & 2), participants were instructed to “allow yourself to crave” (Run 1) or “resist the urge to smoke” (Run 2) during smoking image exposure. Unique, task-driven ROIs for “crave” and “resist” were selected for each individual [peak BOLD response in the prefrontal cortex (PFC), minimum t -value = 3.0, $k = 4$, corrected clusters]. During Neurofeedback runs (Runs 3 & 4) participants received simultaneous feedback via two thermometers following five smoking blocks, each independently driven by activity in the ROIs. Participants were instructed to decrease the level of the “crave” thermometer and increase the level of the “resist” thermometer. Self-reported craving was assessed before and after each run (1–10 scale).

T_1 -weighted images were acquired for each participant (TR = 1750 ms, TE = 4 ms, 1.0 mm isotropic voxels, 160 slices, Siemens 3 T TIM Trio). The four fMRI runs were then acquired (EPI, TR = 2.2 s, TE = 35 ms, 64×64 matrix, 3 mm isotropic voxels, 271 volumes). Turbo-Brain Voyager (TBV) 2.0 software was used for real-time in-scan processing. As in prior studies, the resultant signal estimate within the selected ROI (calculated within 1 TR) was averaged across TRs within a block of smoking cues and “fed back” to the participant at the end of each block ($n = 5$ blocks) using the thermometer display (Hartwell et al., 2011; Li et al., 2012). Blocks of intermittent feedback (versus continuous) were chosen based on prior work (Johnson et al., 2012).

Image preprocessing included: temporal realignment, spatial normalization (Montreal Neurological Institute template), smoothing (isotropic 8 mm³ Gaussian kernel), and high-pass filtering (128 s) (SPM8). The data were modeled with three conditions (smoke, neutral, and rest). The percent signal change was calculated from average BOLD time series within the patient-tailored ROIs (Matlab 7.3, Natick, MA).

3. Results

Sixty percent of the enrolled individuals completed all three visits. There was a significant interaction between completion status (completers and noncompleters) and craving scores before and after instructions to resist (without neurofeedback, ROI Isolation Run 2) ($F(1, 13) = 6.50, p = 0.02$). Following instructions alone, the noncompleters ($M = 3.83$) were able to lower their craving response to cues more effectively than the completers ($M = 6.11$), suggesting that individuals completing the study had a greater need for assistance with craving-reduction via neurofeedback.

3.1. Efficacy of feedback from “crave” versus “resist” ROI

The user-tailored ROIs for the “crave” and “resist” ROI Isolation runs were located in the vicinity of the ventral anterior cingulate cortex (vACC) and the dorsal medial prefrontal cortex (dmPFC), respectively (Fig. 1A). During neurofeedback runs, participants were able to successfully modulate activity in the crave ROI (from Run 1, largely in the vACC ($t(8) = -2.24, p = 0.03$)) but not the resist ROI (from Run 2, largely in the dmPFC ($t(8) = 0.99, p = 0.18$)) (Fig. 1B). When participants viewed smoking cues during the neurofeedback runs, blood oxygen level-dependent (BOLD) activity in the vACC ROI was correlated with self-reported craving following each smoking block (1–5 scale, Spearman's $\rho = 0.55, p = 0.04$). This relationship was not present with neurofeedback from the dmPFC ($p = 0.13$). Thus, a decrease in activity in the vACC, during feedback relative to baseline, was related to a decrease in craving. This was not associated with any demographic or smoking-related variables.

3.2. Effect of runs and visits

Across visits craving scores following the first feedback run (Run 3; $M = 4.82$) were lower than those following the second (Run 4; $M = 5.76$) $p = 0.04$. Compared to instructions to crave (Run 1; $M = 6.00$), neurofeedback was most effective at reducing craving during Visit 3 (Run 3; $M = 4.78$), $t(8) = 2.55, p = 0.03$. There was no significant difference between the feedback runs within a Visit.

4. Discussion

The present study demonstrates the feasibility of an emerging treatment tool, rtfMRI feedback, to help nicotine-dependent cigarette smokers reduce their behavioral and brain responses to cues. These treatment-seeking smokers were able to *decrease activity in a brain region activated by “craving”* (notably the vACC) more effectively than to *increase activity in a brain region activated by instructions to “resist”* the urge to smoke (notably the dmPFC). This finding is buttressed by a correlation between vACC activity and self-

reported craving through the neurofeedback sessions that was not present with feedback from the dmPFC.

The link between ACC activation and craving is consistent with the observation that cigarette cue-induced ACC activation and self-reported craving are attenuated by the smoking cessation medication bupropion (Brody et al., 2004). Together these results suggest that ACC activation and craving can be reduced by both neurofeedback and medication. The ability to modulate ACC activation in response to neurofeedback is not unique to addiction (Hamilton et al., 2011), suggesting that it might be a particularly efficacious target region for rtfMRI studies in other psychiatric populations.

To advance rtfMRI as a treatment for substance use disorders, it is critical to determine the optimal “dosing” of the feedback sessions. Of the participants that completed this study (60%), the benefit of neurofeedback was maximized during the third visit. Although this is encouraging, the low completion rate precludes our ability to make definitive statements about the efficacy of multiple visits. We are currently exploring other potential predictors of ability to modulate neural activity in response to rtfMRI such as the response to peripheral biofeedback and “mindfulness”.

While the conclusions of this study are limited by the small sample and high drop-out rate, the most appropriate control for rtfMRI studies also needs a further study. In an earlier study, for example, we found that using false feedback as a “control condition” led to globally elevated activity in the prefrontal cortex potentially due to frustration (Johnson et al., 2012). Finally, one of the most important issues to be addressed in this field is whether the ability to modulate craving in the MRI scanner can be generalized to the natural environment. This is an essential issue in determining the potential therapeutic benefit of rtfMRI in treating nicotine dependence. With the limitations in mind, these data provide valuable practical advances to support future clinical trials in this emerging area.

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Fig. 1.

Percent signal change in the ROIs during neurofeedback runs. (A) During the ROI isolation runs, participants were instructed to “allow yourself to crave” (Run 1) and then “resist the urge to smoke” (Run 2). Clusters of peak activity during Run 1 (red) and Run 2 (blue) for all individuals have been combined for this figure to demonstrate the spatial distribution. (B) During the neurofeedback runs, participants were instructed to use the feedback to decrease the “crave” ROI (red) and increase the “resist” ROI (blue) in response to cues (which appeared in blocks). These data display percent signal change to smoking (versus neutral

cues) in the ROIs through each feedback block. The data shown are for the nine completers and are collapsed across feedback run and visits. Error bars are one standard error.

*Difference score between blocks significant at $p < 0.05$ (a) and (b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)