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Real-time fMRI in the Treatment of Nicotine Dependence: A Conceptual Review and Pilot Studies

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Abstract

Technical advances allowing for the analysis of fMRI results in real-time have led to studies exploring the ability of individuals to use neural feedback signals to modify behavior and regional brain activation. The use of real-time fMRI (rtfMRI) feedback has been explored for therapeutic benefit in a number of disease states, but to our knowledge the potential therapeutic benefit of rtfMRI feedback in the treatment of addictive disorders has not been explored. This manuscript will provide an overview of the development of rtfMRI and discussion of its potential uses in the treatment of addictions. We also describe a series of pilot studies that highlight some of the technical challenges in developing a rtfMRI feedback paradigm for use in addictions, specifically in nicotine dependence. Because the use of rtfMRI feedback is in its infancy, the work described is focused on establishing some of the basic parameters in optimizing the rtfMRI feedback, such as the type of feedback signal, region of interest for feedback and predicting which subjects are most likely to respond well to training. While rtfMRI feedback remains an intriguing possibility for the treatment of addictions, much work remains to be done in establishing its efficacy.

Keywords

real-time fMRI; real-time fMRI feedback; neurofeedback; nicotine dependence

Development of Real-time fMRI Feedback: An Overview

For the past decade, magnetic resonance imaging (MRI) has been the dominant imaging tool for brain research. Unlike older brain imaging techniques such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), MRI does not use ionizing radiation so it is a relatively low-risk procedure that can be conducted repeatedly without fear of increasing radiation load. In addition, MRI has high spatial resolution and allows for imaging the entire brain in only a few seconds. Initially, MRI was used to examine the structure of the brain, and PET or SPECT were the “tools of choice” for imaging the brain function. However, in the mid-1990’s using a technique called blood oxygen level dependent imaging (BOLD), researchers discovered that they could use MRI to image a variant of hemoglobin that changed locally reflecting different activity of the brain. This finding allowed MRI studies to gather information about brain function (fMRI) as well as structure. Because BOLD changes are not very large (approximately 0.5–3% of baseline), early functional MRI studies (fMRI) could not make statements about a single individual. It was necessary to pool data across multiple individuals because only group data had

sufficient statistical power to be predictive or replicate. With advances in MRI gradient power, it became possible to analyze individual data to determine brain regional activation. However, because fMRI image analysis required massive amounts of computer time, it could not be conducted while the individual was in the scanner.

Recent improvements in image data analyses allow brain activity to be computed almost instantaneously and displayed on an image in the control room of the MRI scanner. These advances have enhanced visualization of changes in brain activity in “real-time”, as an individual performs a task. More recently, it has been possible to summarize regional brain activity and ‘feed back’ information about the activity to an individual in the scanner. This process of performing a functional MRI scan, analyzing the activity immediately (real-time) and providing this feedback to the individual in the scanner is called real-time feedback fMRI (rtfMRI). A more in-depth discussion of the development of rtfMRI and early applications can be found in several recent review articles (Caria 2011, LaConte 2011, and Weiskopf 2011).

Early Studies using rtfMRI

A number of investigators have used rtfMRI to explore the ability of individuals to use neural feedback signals to modify behavior and regional brain activation (Bagarinao, Nakai, & Takana, 2006; Caria et al., 2007; Weiskopf, et al., 2007; deCharms 2008; Lactone 2011). The use of rtfMRI feedback has been explored for therapeutic benefit in various disease states including pain (deCharms et al., 2005), tinnitus (Haller, Birbaumer, & Veit, 2010), and anxiety disorders (Caria, Sitataram, Veit, Begliomini, & Birbaumer, 2010). Recent data suggest that modulation of neural activity based on biofeedback can lead to changes in cognitive and motor performance (Johnson et al., 2010; Johnston et al., 2010; Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011), pain perception (deCharms et al., 2005), and language processing (Rota et al., 2009). While electroencephalographic (EEG) biofeedback procedures have demonstrated some promise in the treatment of addictions (Sokhadze, Cannon, & Trudeau, 2008), the potential therapeutic benefit of real-time fMRI feedback in the treatment of addictions has not been explored.

Development of Real-time fMRI Neurofeedback in Nicotine Dependence

Rationale for the use of rtfMRI in Nicotine Dependence

Nicotine dependence is a significant public health concern. The 2008 World Health Organization (WHO) Report on the Global Tobacco Epidemic estimates that 100 million people worldwide died of tobacco-related causes in the 20th century making tobacco use the leading preventable cause of death in the world (WHO, 2008). In the United States, cigarette smoking continues to be among the leading causes of preventable illness and death in the United States resulting in approximately 443,000 deaths each year (CDC, 2010). Although most smokers want to quit, the vast majority of smoking quit attempts end in a return to smoking (Hughes, Keely, & Naud, 2004). Cigarette smoking estimates decreased dramatically between 1974 and 2005, but then reached a plateau (SAMHSA, 2007) suggesting that progress in smoking cessation may be stalled and innovative approaches to treatment are needed.

One particularly salient feature of abstinence from nicotine is the ability of associated environmental cues to elicit craving and nicotine-seeking behaviors. Craving to smoke during a quit attempt is a robust predictor of relapse (Killen & Fortmann, 1997; Shiffman et al., 1996; Shiffman et al., 1997). Thus, the concept of craving is an important focus of studies on smoking behavior, relapse and smoking cessation treatment.

Developing rtfMRI Feedback Methodology

A number of important methodological decisions were involved in our development of a paradigm to provide nicotine-dependent individuals with real-time fMRI feedback regarding their brain activation in response to cigarette cues. One fundamental decision involved the timing of feedback delivery within the fMRI session. EEG feedback studies have traditionally used a continuous schedule of feedback delivery (Rockstroh, Elbert, Birbaumer, & Lutzenberger, 1990), whereas rtfMRI investigations have used either an intermittent (Yoo & Jolesz, 2002) or a continuous feedback schedule for participant training to account for the intrinsic delay between neural events and hemodynamic response (deCharms et al., 2005; Weiskopf et al., 2004; Caria et al., 2007). Although continuous feedback provides participants with maximal information about their brain function, continuous feedback may hamper participants' neurofeedback performance by imposing an excessive cognitive load. Specifically, in continuous feedback rtfMRI, participants must link feedback to cognitive events that occurred several seconds prior and must simultaneously evaluate feedback while engaging in an experimental task. A second fundamental issue concerns the appropriate control condition. Most studies have either used a no-feedback (Caria et al., 2007; deCharms et al., 2005; Johnston et al., 2011) and/or a "false-feedback" control condition, in which participants are provided with feedback from non-targeted brain regions or from other participants (Caria et al., 2007; deCharms et al., 2005; Hamilton et al., 2011; Rota et al., 2009). While a no-feedback condition may not adequately control for all non-essential task processes (e.g., the process of evaluating feedback), a false-feedback condition may produce unintended frustration and/or increased/expanded efforts to control brain activity.

To explore these issues, we conducted a study to determine the relative merits of intermittent vs. continuous feedback, as well as the impact of false vs. real feedback on participants' brain activity (Johnson et al., 2010). Thirteen healthy ($F=6$), non-smoking, right-handed volunteers completed four runs of an "imagine movement" block-designed scan where they were asked to imagine moving their right hand while the hand was in a physical restraint, when the word "IMAGINE" was displayed, or to engage in non-movement thoughts, when the word "REST" was displayed. The four imagine movement scans were conducted using a randomized cross-over design (intermittent or continuous feedback delivered as a thermometer signal crossed with real or randomly generated false feedback: Intermittent Real [IR], Intermittent False [IF], Continuous Real [CR], Continuous False [CF]). Baseline localizer scans during which participants engaged in the imagine movement task without feedback, were used to isolate regions of interest (ROI) in the premotor cortex. During "real-feedback" blocks, participants viewed their BOLD activation to imagined movement derived from their individually determined ROI. During "false-feedback" blocks, participants viewed randomly generated feedback unrelated to their fMRI signal. For continuous scans, a thermometer display of participants' ROI activation to imagined movement (vs. rest) was updated with each incoming volume and displayed throughout the IMAGINE condition; an inactive thermometer was displayed throughout the REST condition. For intermittent scans, no thermometer was displayed during IMAGINE or REST conditions; instead the last volume of the IMAGINE block and the first volume of the REST block was replaced with an active thermometer display.

As can be seen in Figure 1, with continuous feedback, participants had significantly lower ROI activation during real-feedback vs. false-feedback or baseline (i.e., no-feedback) scans. This suggests that continuous feedback did not improve participants' ability to increase imagined movement-related brain activity (relative to false or no feedback). Conversely, during intermittent feedback, participants had a significantly higher ROI activation during real-feedback vs. false-feedback or baseline (i.e., no-feedback) scans. In other words, real, intermittent feedback improved participants' ability to increase imagined movement-related brain activity. Interestingly, follow-up whole-brain analyses further demonstrated that false

feedback produced a widespread pattern of activation involving frontal, temporal, and parietal regions, a distinctly different pattern than the more localized activation associated with real-feedback. Based on these findings, we decided to utilize intermittent feedback and a no-feedback control condition in our subsequent work with rtfMRI in nicotine-dependent individuals.

Imaging Craving and Resisting in Nicotine Dependence

In order for a behavior or cognition to be targeted for rtfMRI, it must be possible to image the regional brain activity associated with it using fMRI. A number of neuroimaging studies have examined regional areas of brain activation associated with craving during the presentation of smoking-related cues in nicotine-dependent individuals. Exposure to smoking-related cues commonly provokes activation in regions subserving attention such as the anterior cingulate cortex (ACC), precuneus, and cuneus (Brody et al., 2002; Brody et al., 2007; McClernon & Rose, 2005; Smolka et al., 2006; Wilson, Sayette, Delgado, & Fiez, 2005); the mesolimbic dopamine reward system known to be activated by addictive drugs including the right posterior amygdala, posterior hippocampus, ventral tegmental area, and medial thalamus (Due, Huettel, Hall, & Rubin, 2002); and regions involved in decision making and goal directed behavior such as the prefrontal cortex (PFC) (Hartwell et al., 2011; Lee, Lim, Wiederhold, & Graham, 2005).

To date, only two studies have reported on regional brain activation associated with resisting the urge to smoke during presentation of smoking cues. During attempts to resist the urge to crave, relative to neutral epochs, Brody and colleagues (2007) found activation in the dorsal ACC, secondary visual processing centers (bilateral precuneus, left angular gyrus, and bilateral supramarginal gyri), posterior cingulate cortex (PCC), and bilateral retrosplenial area. During attempts to resist craving, relative to craving epochs, there was increased activation in the left dorsal and perigenual ACC, left posterior cingulate cortex (PCC), and left precuneus; areas involved in decision making, attention, motivation, and visual processing. Further exploration by our group demonstrated activation of the left ACC and areas of the left PFC (Figure 2), regions associated with executive function, during attempts to resist the urge to smoke (Hartwell et al., 2011). In contrast to the findings of Brody and colleagues (2007), our group found considerable overlap between the areas activated during craving and attempts to resist craving suggesting that attempting to resist craving is almost always accompanied by some amount of craving and vice versa (Hartwell et al., 2011).

Considerations in Choosing a Region of Interest for rtfMRI in Addictions

There are a host of additional issues to be addressed in using real-time fMRI feedback for craving reduction. One critical issue involves the decision concerning the brain region activation that is displayed to subjects. The region of choice could be based on structural anatomy or on the subjects' brain activation while performing the task in question (craving or resisting the urge to crave). A second issue is whether to ask subjects to increase blood flow (BOLD activity) to regions that appear to be associated with resisting the urge to crave or to decrease blood flow to regions that are activated during craving. While we decided to generally focus on brain regions that we found in prior imaging work to be involved in either craving, or in attempting to resist craving, we allowed the exact choice of the region of interest (ROI) for feedback purposes to be guided by the subject's activation during a baseline fMRI scan. Thus, we used a hybrid approach with a definite hypothesized region and direction of needed change, and then guided the final placement based on individual response. At this point, it is not clear that it is necessary to guide ROI decisions based on individual activation or if one could simply be guided by anatomy or prior group results. The above choices and issues have prompted some investigators to abandon the use of predefined regions and use instead non-hypothesis driven whole brain approaches to

feedback. In this work, the entire brain is considered and maps are acquired in one state (e.g. craving) and then another (rest). Machine vector learning or other advanced statistical approaches are then used to analyze the entire brain, predict what are the key or essential elements in that state and then feedback to the subject how close they are in making their brain ‘resemble’ or approximate a given state (Brown et al., 2011; Deshpande et al., 2010). This is clearly an area that warrants further exploration.

Predicting Response to Feedback

Because we observed considerable variability in subjects’ abilities to manipulate neural activity based on feedback, we decided to explore the idea of enriching our sample by trying to identify those subjects who are more likely to be able to manipulate their neural activity based on rtfMRI feedback. We have been investigating performance in simple biofeedback tasks conducted outside of the scanner as a potential predictor of real-time fMRI feedback performance. Our first ten healthy ($F=3$), adult, treatment-seeking, nicotine-dependent smokers completed a standard 10-minute continuous skin temperature biofeedback task, outside of the scanner, prior to participating in the rtfMRI feedback paradigm described in the subsequent section, Crave and Resist Feedback in Nicotine-Dependent Cigarette Smokers. Skin temperature biofeedback, which teaches patients to increase their finger temperature via voluntary arteriole vasodilatation, has demonstrated efficacy for the treatment of Reynaud’s disease, headaches, and various other conditions (Yucha and Montgomery, 2008). Performance on the biofeedback task was quantified as the difference in skin temperature between the final 30 seconds of the task and the first 30 seconds of the task. Across participants, there was a small, non-significant increase in skin temperature from the first ($M = 90.14$, $SD = 3.46$) to the last ($M = 90.54$, $SD = 4.53$) 30 seconds of the task ($t [9] = 0.50$, $p = 0.63$). Participant’s rtfMRI performance was quantified as the difference in BOLD signal (i.e., % signal change using rest as the comparison condition), within functionally identified brain regions of interest (i.e., ACC for the “reduce craving” scan and right mPFC for the “resist craving” scan), between the last and the first block of smoking pictures within a given feedback scan. The association between biofeedback and rtfMRI feedback response was investigated using correlational and multiple regression analyses (Figure 3). Correlational analyses demonstrated that rtfMRI feedback performance for the “reduce craving” feedback scan was significantly correlated with ability to raise finger temperature (Spearman’s $r = -0.69$, $p = 0.03$). In multiple regression analyses, biofeedback explained a significant portion of variance in change in craving-related BOLD signal during the “reduce craving” scan ($R^2 = 0.62$, $F (2, 7) = 5.73$, $p = 0.03$); and biofeedback significantly predicted change in craving-related BOLD signal ($\beta = -0.08$, $t (9) = -2.87$, $p = 0.02$), controlling for initial craving-related BOLD signal ($\beta = -0.48$, $t (9) = -2.53$, $p = 0.04$). Conversely, for the “increase resistance” scan, there was no association between participants’ rtfMRI performance and their biofeedback performance (Spearman’s $r = 0.15$, $p = 0.68$). Although these findings are preliminary, they suggest that skin temperature biofeedback testing may be a useful tool for identifying individuals who are most likely to be able to manipulate neural activity in response to rtfMRI feedback. We continue to collect skin temperature biofeedback data on all rtfMRI participants and further analyses of the association between biofeedback and rtfMRI performance are planned.

Reference Block

Research has demonstrated that the BOLD fMRI signal is associated with neural activity (primarily local field potentials; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), but provides only an *indirect* measure of neural activity that is quantified in arbitrary MR units. As a result, the BOLD signal during a given condition or stimulus can only be meaningfully interpreted in reference to the BOLD signal during a second condition or stimulus. In developing our rtfMRI paradigm, we initially chose to use the “rest” (i.e., cross-

hair fixation) condition as a natural baseline from which to evaluate changes in cue-elicited craving during feedback conditions. More recently, however, we have decided to use a “craving” condition (where participants view smoking cues for 60 seconds, at the beginning of each feedback scan, with the instruction, “allow yourself to crave”) as our baseline. We made this change because of a potential ceiling effect in many participants’ feedback data. Specifically, because craving-related brain activity was relatively low during rest conditions, participants’ were often not able to further reduce their craving-related brain activity during feedback conditions. Changing our baseline condition from rest to “craving” should eliminate this potential ceiling effect and provide participants with a more clinically relevant baseline from which to modulate their cue-elicited craving. That is, our ultimate goal is to teach patients to reduce their craving in circumstances where they are experiencing some degree of craving (e.g., the “craving” condition), as opposed to periods when they are experiencing low levels of craving (e.g., the “rest” condition). Data collection and analysis using the new “craving” baseline condition are ongoing.

Crave and Resist Feedback in Nicotine-Dependent Cigarette Smokers

Our earlier work identified regional activation patterns while smokers were actively craving and attempting to resist craving in response to exposure to smoking-related cues. We were interested in comparing the ability of smokers to reduce craving and increase resisting the urge to smoke with realtime neurofeedback. As a next step, we examined the ability of the same 10 smokers from the group described in the Predicting Response to Feedback section to: (1) reduce craving in the presence of smoking cues and manipulate a thermometer driven by activity in the ACC; and (2) increase resistance to craving during smoking cue presentation and manipulate a thermometer driven by activity in the middle prefrontal cortex (mPFC) in one imaging visit following the laboratory temperature biofeedback session. The regions of interest (ROIs) for feedback were captured during baseline exposure to blocks of smoking-related visual cues, neutral cues, and rest following handling and smelling a preferred brand cigarette with the instructions to either “allow yourself to crave” or “resist the urge to smoke” when presented with the smoking-related cues. Three-slice ROIs were selected for neurofeedback in the ACC and mPFC ($t=3$, cluster threshold size = 4) towards the end of the baseline crave and resist scan, respectively. During feedback runs, a thermometer reflecting activation in the ROIs was presented at the end of each smoking cue block. The thermometer reading was generated from an analysis computer running TurboBrain Voyager (TBV) software linked to the presentation system. The thermometer measure reflected the maximum percent signal change for the ROI utilizing a general linear model (ROI-GLM) for baseline estimation and a dynamic ROI (top 33% of best voxel selection) to create a sub-ROI for maximal signal extraction from the coarse anatomical ROI adjusting for small alignment errors within and between scans.

Subjects were able to significantly reduce subjective ratings of craving ($p=0.002$) and BOLD activation in the ACC ($p=.028$) in the ‘reduce craving’ biofeedback scan compared to baseline (Figure 4). Decreased ACC activation was significantly correlated with mean craving ratings during feedback ($r=0.957$, $p=0.011$) indicating that larger decreases in ACC activation were associated with greater reductions in subjective craving measures. No differences were found in the mPFC BOLD signal nor subjective craving ratings between the baseline resist and ‘increase resistance’ neurofeedback scan. During the baseline crave scan (Figure 5), increased activation was found in the smoking-cue condition compared to rest in ACC, frontal cortex, nucleus accumbens, hippocampus, parietal cortex and bilateral occipital cortex (random effect analysis; $p < 0.005$, cluster size 10 voxels). Utilizing the same threshold, during the “reduce craving” feedback condition, no activated regions were found. In contrast, analysis of “resist craving” found activation in the medial frontal cortex, bilateral middle frontal cortex, bilateral insula, thalamus, and bilateral cortex during the

baseline resist scan with the same contrast and statistical threshold. Neurofeedback did not significantly increase the BOLD signal in the targeted region. However, increased activation, during neurofeedback while “resisting craving,” was noted in the middle cingulate, parietal, and occipital cortex. Additionally our previous work suggested that craving and resisting the urge to smoke are closely related; with craving associated with some degree of resisting the urge to smoke, and resisting is almost always accompanied by a degree of craving. Driven by the results of this small pilot project, further development efforts focused on an integrated approach of providing simultaneous feedback from the ACC and mPFC. With respect to the direction of change and number of regions used in the feedback task, in a subsequent exploratory paradigm we gave subjects feedback from two different regions displayed on two separate thermometers simultaneously. Sixteen healthy ($F=10$), adult, treatment-seeking, nicotine-dependent smokers were newly recruited for this phase. The number of participants was increased with the intention of improved statistical power to detect small changes in the BOLD signal. One thermometer reflected activity in regions associated with increasing resistance and subjects were instructed to increase the thermometer reading. The other thermometer was inversely related to activity in brain regions associated with craving, so while subjects were also instructed to increase this thermometer reading, increases were associated with decreases in blood flow in the specified regions. Although the sample size was small ($N=16$), we found that the subject’s performance with the two thermometer paradigm was worse than with a single thermometer. The reasons for this are not clear. It is possible that it is too difficult for subjects to attend to two thermometers simultaneously, so the complexity of the task had a negative impact on performance. In any case, in the on-going clinical trial we have decided to use only one feedback thermometer associated with regions activated during craving.

The results suggest that nicotine-dependent cigarette smokers may be trained to exert voluntary control over the ACC in response to rtfMRI feedback by actively trying to reduce the urge to smoke. These same smokers were less successful in increasing activation in the mPFC in response to neurofeedback while trying to increase resistance to the urge to smoke. It may be that through neurofeedback training, the ACC becomes decoupled from the reward network. Volitional control of the ACC demonstrated in this project adds to previous research regarding the role of the ACC in craving and drug addiction. Previous research has shown that one of the mechanisms of action of bupropion, a first-line smoking cessation medication, is to reduce subjective craving and ACC activation during cue exposure (Brody et al., 2004). Additionally surgical lesioning of the ACC has been shown to reduce drug use among alcohol and opioid dependent individuals (Kanaka & Balasubramaniam, 1978). These findings clearly identify the ACC as an area warranting further study in the context of nicotine dependence.

Future Directions

We now have a paradigm in which nicotine-dependent smokers appear to be able to use rtfMRI feedback to help them decrease the neural activity associated with cue-induced craving. We plan to test the applicability of this training in assisting individuals in smoking cessation. This brings up a different set of methodological issues. For example, the optimal “dose” of rtfMRI has not been determined. It is not clear whether more sessions and practice would improve learning. If multiple sessions are to be tested, the amount of time between sessions must also be determined. Further, it may be that rtfMRI could serve as a tool to help people identify strategies to reduce cravings, but that practice outside of the scanner, in the real world, might be an important factor in determining whether the techniques learned ultimately affect behavior. The use of instructions is also an area that requires exploration. While some studies have shown that performance improves when subjects are provided with training and instructions (Scharnowski et al., 2004; Weiskopf et al., 2004), in one

biofeedback study specific instructions concerning heart rate control were deleterious (LaCroix & Roberts, 1978). Finally the transferability of the training to situations outside of the scanner and the durability of the training are also areas that warrant exploration.

Conclusions

In conclusion, the use of real-time fMRI feedback in a variety of pathologic states is the subject of a growing number of investigations. The potential clinical applications for rtfMRI are numerous. Disorders associated with a well-delineated regional BOLD brain activation pattern are excellent candidates for the application of rtfMRI neurofeedback. Promising preliminary investigations include pain (deCharms 2005), emotion regulation (Caria 2010, Posse 2003), linguistic processing (Rota 2011), and brain-computer interface for control of a robotic arm (Lee 2009) among others. Real-time fMRI neurofeedback has the advantage of being non-invasive, the capacity to target very specific brain regions, and minimal adverse effects compared to pharmaceutical treatments. Real-time fMRI neurofeedback has the potential of offering alternative interventions for challenging chronic illnesses and the development of new technologies for new approaches. Our preliminary work shows promise in the use of real-time fMRI feedback in helping nicotine-dependent individuals exert voluntary control over urges to smoke. However, a number of fundamental methodological issues need to be addressed in order to establish “best practices” in the use of real-time fMRI feedback in general and, more specifically, for its use in the treatment of addictive disorders. Both the parameters used in the rtfMRI feedback sessions and the procedures for transitioning from performing the task within the scanner to “real world” applications need to be studied. However, using rtfMRI feedback in the treatment of addictions is an innovative approach which has enormous potential for increasing our knowledge about the basic neural processes underlying addictions and improving treatment outcomes.

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Figure 1.

Mean Percent Signal Change of Best Voxel from Individually Selected Region of Interests. A region of interest was selected for each individual from a baseline scan. The mean percent signal change across individuals from the best voxel (highest z value) in the individual region of interest is plotted for the Continuous Feedback paradigm (top left) and for the Intermittent Feedback paradigm (top right). The hemodynamic rest (and intermittent feedback) periods are shaded and the “Imagine Movement” periods are unshaded in the plots, comparing the baseline scans (dotted gray line), real feedback scans (thick black line), and false feedback scans (thin gray line). Bottom Left: For the Continuous Feedback paradigm, the percent signal change during “Imagine Movement” for Real Feedback scans was significantly less than for Baseline ($p < .01$, Bonferroni corrected) and False feedback scans ($p < .001$, Bonferroni corrected). Bottom Right: For the Intermittent Feedback paradigm, the percent signal change during “Imagine Movement” for Real Feedback scans was significantly greater than for Baseline and False feedback scans ($p < .001$ for all pairwise comparisons, Bonferroni corrected). Reproduced, with permission from Johnson et al (2010).

Figure 2. fMRI results comparing smoking-related to neutral cues during Crave Condition (red) and Resist Condition (blue). Reproduced, with permission, from Hartwell, et al., 2011.

Figure 3.

Correlations between change in finger temperature during biofeedback and percent BOLD signal change during neurofeedback.

Left: Change in finger temperature during biofeedback was significantly, negatively correlated with change in BOLD signal during “reduce craving” neurofeedback ($r = -0.69, p = 0.03$), suggesting that participants with the largest increases in skin temperature during biofeedback were most successful in reducing, or minimizing increases in, their craving-related brain signal during “reduce craving” neurofeedback.

Right: Change in finger temperature during biofeedback was not significantly associated with change in BOLD signal during “resist craving” neurofeedback ($r = 0.15, p = 0.68$).

Figure 4.
ACC activation in response to feedback ($p=0.028$)

Figure 5.

Top: ACC during baseline craving and feedback to reduce craving; Bottom: right mPFC during baseline resisting and feedback to increase resistance (random effects analysis, $p < 0.005$ uncorrected with extent cluster threshold 10 voxels).