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Individual variability in the locus of prefrontal craving for nicotine: Implications for brain stimulation studies and treatments

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Abstract

Background—Attenuation of cue-elicited craving with brain stimulation techniques is a growing area of attention in addiction research. This investigation aims to guide these studies by assessing individual variability in the location of peak cortical activity during cue-elicited craving.

Method—Twenty-six nicotine-dependent individuals performed a cue-elicited craving task in a 3T MRI scanner while BOLD signal data was collected. The task included epochs of smoking cues, neutral cues, and rest. The location of peak activity during smoking cues relative to neutral cues ('hot spot') was isolated for each individual. The spatial dispersion of the 26 cue-elicited hot spots (1 per participant) was quantified via hierarchical clustering.

Results—When viewing nicotine cues all 26 participants had at least one cluster of significant prefrontal cortex activity ($p < 0.05$, cluster corrected). Only 62% had peak activity in the medial prefrontal cortex cluster (including 100% of the men). In 15% of the participants peak activity was located in either the left lateral prefrontal cortex or left insula cluster. Peak activity in the remaining 23% was dispersed throughout the prefrontal cortex.

Conclusion—There is considerable individual variability in the location of the cue-elicited 'hot spot' as measured by BOLD activity. Men appear to have a more uniform location of peak BOLD response to cues than women. Consequently, acquiring individual functional imaging data may be advantageous for either tailoring treatment to the individual or filtering participants before enrollment in treatment.

Keywords

nicotine; craving; functional MRI; transcranial magnetic stimulation

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1. Introduction

Despite large public health initiatives and advances in pharmacotherapeutic options for treating dependence, 21% of Americans remain nicotine dependent (NCCDP, 2010). Although the rates of individuals seeking treatment has risen, approximately 75% of treatment-seekers relapse within the first 10 days (Hughes et al., 2004).

Cue-induced craving is a significant predictor of relapse (Killen and Fortmann, 1997; O'Connell et al., 2010). Recent interest has developed in whether one can attenuate this cue-elicited craving through brain stimulation techniques such as transcranial magnetic stimulation (TMS) (Amiaz et al., 2009; Eichhammer et al., 2003; Rose et al., 2011). The location of optimal rTMS stimulation to attenuate cue-elicited craving, however, remains elusive. While rTMS in the left dorsolateral PFC has been shown to decrease craving (Amiaz et al., 2009), another study revealed no effect (Eichhammer et al., 2003). Although the medial prefrontal cortex (mPFC) is strongly related to craving and is modulated by craving intensity (Hartwell et al., 2011; McClernon et al., 2005), rTMS of the superior frontal cortex in the vicinity of the mPFC, however, actually increased craving (Rose et al., 2011).

It is possible that, among several factors, the mixed results in these studies are due to large individual variability in the cortical regions involved in craving. For example, within the fairly uniform anatomy of the motor strip, the best location to stimulate to move the thumb varies over 2cm³ among individuals. In the case of craving, a uniform prefrontal locus of stimulation may not be optimal for all individuals. Information from functional imaging techniques may be necessary to tailor treatment location to the individual smoker. The primary aim of this investigation was to determine the spatial variability in peak cortical activity during cue-elicited craving. A secondary aim was to calculate whether observed population variability could be captured by a single site of TMS stimulation or if it requires within-individual functional mapping.

2. Method

The participants were a subset (n= 26) of nicotine-dependent individuals between 25–45 years old recruited to participate in a larger functional MRI study of cue-induced craving (Hartwell et al., 2011). Participants were recruited from the local community and all subjects signed a written consent approved by the Medical University of South Carolina (MUSC) IRB. All participants were right handed and met DSM-IV criteria for nicotine dependence. Demographic and smoking behavior data recorded (average $\pm$ SD) included age (31 ± 3.7), male:female count (14:12), cigarettes per day (15.2 ± 5.3), Fagerstrom Test of Nicotine Dependence (5.3 ± 1.7 ; Fagerstrom 1978), cigarette craving at the time of scanning (6.5 ± 1.4 ; Questionnaire of Smoking Urges-brief, Cox et al. 2001) and exhaled CO levels (11.9 ± 4.4 , following 2 hours of abstinence).

Task and Image Acquisition

All participants were asked to refrain from smoking two hours before the MRI scanning session. Exhaled carbon monoxide levels were measured with a Micro-Smokelyzer (Bedfont Scientific Ltd., Kent, UK) and baseline craving measures were collected before the scan. High-resolution T₁-weighted anatomical images were acquired for each participant (3.0 T Siemens Trio, 3D SPGR, TR=10 ms, TE=3 ms, voxel dimensions 1.0×1.0×1.5 mm, 256×256 voxels, 124 slices). The head was positioned along the canthomeatal line. Foam padding was used to limit head motion T2* weighted imaging data were acquired during two 12 minute runs of the cue-elicited craving task (each run: TR = 2.2, TE = 35 ms, 64×64, 3mm isotropic voxels, 328 volumes). The cue-elicited craving task was based on prior work

(Myrick et al., 2004; Myrick et al., 2008). Briefly, in the MRI environment participants were exposed to blocks smoking-related (e.g., lighters, packages of cigarettes) and neutral pictures (e.g., pencils, dishes), interleaved with rest blocks. Craving was measured before, after, and 8 times within each run of the cue-elicited craving task.

Imaging data were preprocessed using standard statistical approaches (SPM 5, London, UK) and further analyzed with custom scripts (MATLAB 7.0, Natick, MD). The functional data from each participant were corrected for acquisition time (slice timing), realigned to the first volume (motion correction), normalized into a standardized neuroanatomical space (Montreal Neurological Institute brain template, MNI), smoothed using a Gaussian kernel of 8 mm, and high-pass filtered (128s) to remove low frequency noise. Inspection of motion correction revealed that all corrections were less than the 2mm. For each individual voxel-based analysis was performed using the general linear model to assess relative BOLD signal during periods of smoking cues, neutral cues, and rest. Regressors were convolved with the standard hemodynamic response function.

Individual imaging analysis

To investigate individual variability, the primary locus of activity in the during smoking-related relative to neutral cues (“hot spot”) was isolated for each individual by locating the local maximum voxel (x, y, z, MNI coordinates) within the most significant cluster of activity ($p < 0.05$, Bonferroni corrected at the cluster level). The analysis was limited to significant clusters within the prefrontal cortex as this is the area that can be stimulated with current non-invasive TMS studies. The dispersion of the peak locations was determined by calculating the Euclidean distance from each individual’s peak coordinate to the group average. The most significant cluster was used when an individual had more than one significant cluster (4/26).

Hierarchical Clustering

Spatial dispersion of the “hot spots,” were further characterized via agglomerative hierarchical clustering analysis using Ward’s linkage criteria (Kraskov et al., 2005; Krzanowski, 1988). Briefly, the algorithm starts by treating the locations of the hot spots (1 per participant, 26 total) as individual clusters. The distance between each cluster and its neighbors is calculated, and clusters are joined together such that within-cluster variance is minimized. This proceeds iteratively until all 26 points have been grouped. At each iteration the distances between resultant clusters of points (linkage distances) are computed. The results of this clustering procedure are typically displayed in a dendrogram (as in Figure 2). This clustering method was chosen based on prior studies with functional MRI data (Dimitriadou et al., 2003).

Following the hierarchical clustering procedure, posthoc tests were performed to determine whether classification of a “hot spot” within the mPFC cluster was associated with demographic and smoking use variables (age, gender, cigarettes per day, Fagerstrom Test of Nicotine Dependence (FTND) score, and cigarette craving at the time of the scan; IBM SPSS Statistics ver.19). The significance level of $p < 0.05$ was used. One-way analysis of variance was used for the continuous variables (age, cigarettes per day, FTND score, craving) with classification in/out of the mPFC cluster as the independent variable. A Chi-square test was used to assess the categorical variable (gender).

3. Results

Group Analysis

For the group, the largest difference in brain activity when viewing smoking-related relative to neutral cues was in the mPFC (X, Y, Z: -4, 44, 2, corrected cluster $p = 0.028$, cluster size 152 voxels; Figure 1a).

Individual analysis

All 26 participants had at least one cluster that reached significance in the prefrontal cortex when viewing the smoking-related relative to the neutral cues ($p < 0.005$, uncorrected clusters) (Figure 1b). This location was lateralized to the left hemisphere in 18/26 individuals. The arithmetic mean of all 26 points was located at -6, 41, 0 (BA 10). Hot spots were located in the left hemisphere for 18/26 individuals (mean: -20, 41, -5; BA 11) and the right for 8/26 individuals (mean: 25, 40, 11; BA 47). The distance between the lateralized means and the group mean was 15.66mm (left) and 33.28mm (right). The average distance from each individual hot spot to the group voxel-based mean was 4mm among points in the left hemisphere (18/26) and 37mm overall (26/26) (Axis (standard deviation, distance range): X (± 16 mm, 0–57mm), Y (± 9 mm, 0–36mm), Z (± 12 mm, 0–40mm).

Hierarchical cluster analysis of the hot spot locations (1 per individual, 26 total) revealed that 70% of the population variance could be accounted for by 3 clusters. Of the three clusters of hot spots that were generated, one large cluster in the left mPFC dominated the analysis (Figure 2a). The clusters were centered in the left mPFC (-9, 51, -4), left lateral PFC (-31, 20, 25), and the left insula (-34, 5, -33) (Figure 2b). The hot spots for 6 individuals were not placed in a cluster. Five of these had hot spots distributed throughout the right frontal cortex.

Post hoc analyses revealed that classification into the mPFC cluster was related to gender but not to age, cigarettes smoked per day, Fagerstrom Test of Nicotine Dependence score, or cigarette craving during the day of the scan. Men were significantly more likely to have a hot spot in the mPFC than women ($\chi^2 = 4.57$, $p = 0.03$) (Cluster 1: 11/14 men, 5/12 women).

4. Discussion

The data from this study largely confirm prior reports that the medial prefrontal cortex is activated during cue-elicited nicotine craving. By extending this customary analysis to an investigation of patient-specific cue-reactivity however, the data illuminate a large degree of individual variability in the peak, or “hot spot,” of activation. Hierarchical clustering analysis revealed that while the majority of the participants had hot spots in the left mPFC, peak activations for the remaining 38% of the individuals were dispersed throughout the prefrontal cortex, including 2 small clusters in the left lateral prefrontal cortex and insula. Data from this preliminary investigation suggest that, due to the high spatial variability in the locus of peak cue-reactivity, the effectiveness of a stimulation therapy may be maximized by using functional imaging to tailor the TMS focus for each individual. Alternatively, one might choose a scalp location that will work to stimulate craving networks in 68% of individuals, and then use image guidance in non-responders.

This large individual variability may provide insight into the inconsistent outcomes of previous research using TMS for smoking cue-induced craving. An early study demonstrated that one session of 20Hz stimulation to the left dorsolateral PFC (LDLPFC) had no influence on craving (Eichhammer et al., 2003). In contrast, Amiaz and colleagues

(2009) demonstrated that 10 sessions of stimulation (20Hz) to the DLPFC led to significant, though transient, reductions in craving. A recent study selected the medial superior frontal gyrus as a target for stimulation based on functional imaging data (McClernon et al., 2005). Their group then demonstrated that 10 Hz stimulation to this area, which overlaps with Cluster 1 in our study, *increased* craving to smoking cues (Rose et al., 2011). While individual variability in the craving hot spot observed in our investigation may contribute to these mixed results, it is still unclear whether targeting the hot spots for craving directly will maximize therapeutic efficacy.

Implications for brain stimulation

The results of this study provide critical information on the spatial distribution of craving “hot spot” in substance abusers. Moving forward it will be important to determine whether one should choose to stimulate the primary site of craving directly or to apply rTMS to a neighboring regions. More explicitly, should we 1) stimulate at the site of the ‘hot spot’ to *push* the signal down in that area or should we 2) stimulate in a neighboring neural circuit to *pull* the activity away from the ‘hot spot’? From one perspective, we might expect to get maximal, sustained attenuation of cue-induced craving with an extended course of repetitive TMS directly over the hot spot. This hypothesis is supported by prior double-blind sham controlled rTMS studies which have demonstrated that 2–4 weeks of rTMS (relative to sham) is associated with a decrease in blood flow in the region stimulated and an increase in flow in neighboring regions (Teneback et al., 1999). In contrast, attenuation of craving may be best achieved with stimulation of the mesocortical (lateral PFC) rather than mesolimbic (medial PFC) areas, an effort to *pull* the activity away from limbic circuits. Amiaz et al. (2009) for example, found that rTMS to the right lateral PFC attenuated craving which they attributed to increase in cognitive control. They did not, unfortunately, collect neuroimaging data. Recently, Mishra et al (2010) demonstrated that 10 days of rTMS over the right DLPFC (relative to sham TMS) reduced alcohol craving in dependent alcoholics for up to one month after the treatment {Mishra, 2010}. As with Amiaz et al. (2009), the neurobiological explanations of the reduced craving following DLPFC rTMS remain unclear.

It is important to note that the effect of rTMS on brain activity is influenced by several variables other than the site of stimulation, including, but not limited to, the pulse frequency. For example, in one of the first systematic studies of alterations in brain activity associated with rTMS treatment, Speer and colleagues demonstrated that rTMS at 20Hz for 10 days was associated with a sustained *increase* in bilateral blood flow 72 hours after stimulation, while 1Hz stimulation was associated with a sustained *decrease* in blood flow (Speer et al., 2000). This is consistent with prior predictions that the frequency of stimulation is related to relative long term cortical potentiation (Post et al., 1997). This relationship between high/low frequency stimulation and elevated/depressed neural activity however, appears to be dependent upon the cortical area stimulated and the technique used to measure alteration in neural activity (e.g., O¹⁵-PET, FDG-PET, BOLD; George et al., 1999; Kimbrell et al., 2002; Nahas et al., 2001; Paus et al., 1997; Wassermann and Grafman, 1997).

Factors that influence variability

Considered together these data suggest that both 1 Hz stimulation of the medial prefrontal cortex and 10 Hz stimulation at the DLPFC may be candidate protocols for lowering neural activity in the brain regions modulating craving. The results of the present study however suggest that, due to the spatial variability within individuals, this should be chosen on an individual basis rather than a blind average. Although neither age nor use variables were associated with the location of the craving hot spot, gender was a salient predictor. The cue-elicited craving hot spot was located in the mPFC for 79% of men (11/14), but only 42% of

women. Additionally, both of the individuals with hot spots in the left insular cortex were women. These data suggest that nicotine smoking men may have a more uniform response to cue-elicited craving than women.

Limitations

In order to provide some common framework to compare this study to other studies, the anatomical data from all participants was spatially normalized to a standard anatomical template (MNI). Although there was minimal spatial distortion in this cohort of smokers, normalization compromises the spatial precision of these data. Additionally, this cohort contained a large range of cigarettes smoked per day (8–40), years of smoking (2–40) and age (20–55 yrs). It is possible that the individual variability of “hot spots” would be lower with a more uniform cohort.

Although most neuroimaging investigations of cue-elicited craving are interested in patterns of neural activity that characterize a population as a whole, the results of this study demonstrate that there is a large variance in the location of peak brain activity during cue-elicited craving. While the craving hot spots were clustered around the mPFC in 62% of these smokers, hot spots for 38% of the population (predominantly women) were outside of this area. Although acquiring functional imaging data before brain stimulation intervention is more expensive and time-consuming, these data suggest individual imaging may be advantageous for tailoring treatment location or to filter participants before the clinical intervention.

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Figure 1. Variability in peak location of craving

Locations of peak activity during a cue-induced craving task were isolated for nicotine smokers as a group (A) and independently for each individual (B). Considered as a group (A), nicotine smokers had significantly more activity in the medial prefrontal cortex during smoking –related pictures relative to neutral pictures (corrected cluster, $p = 0.02$). When each individual was assessed independently (B) the location of peak activity to smoking related cues spanned multiple brain regions, with the majority of the points in the left hemisphere during smoking related cues (circles, 1 per individual).

Figure 2. Cluster analysis of peak craving locations

A dendrogram of agglomerative hierarchical cluster analysis demonstrates that hot spots for the cue-elicited craving task, could be characterized by 3 clusters. These clusters are within 26mm linkage distances, representing 70% of the population variance (dashed line). The most prominent cluster (red, left) contains 61% of the participants. The second (green, middle) and third clusters (blue, right), both capture another 8% of the participants. The hot spots for 6 individuals did not fall within a cluster (black). The centers of these 3 clusters are displayed (B).