# Brain reactivity to smoking-related cues during tobacco abstinence: an fMRI study.

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**Background:** Nicotine replacement therapies (NRT) are effective at reducing withdrawal symptoms, but they do not blunt cue-induced craving or maintain extended abstinence (Hughes et al., 2003; Tiffany et al., 2000). Identifying the brain substrates that contribute to smoking-related cue reactivity during NRT may help to determine which neural circuits and neurochemical pathways need to be targeted by novel therapeutics.

**Methods:** We used blood oxygen level dependent (BOLD) functional MRI (fMRI) to characterize brain activation patterns in response to smoking-related cues. Nicotine-dependent subjects (N=13) participating in a smoking cessation clinical trial were scanned twice, once prior to becoming abstinent (pre-abstinent: expired carbon monoxide (CO) = 21.7 ± 9.2 ppm) and once during abstinence after 51.5 ± 11.3 days of NRT treatment (expired CO = 1.7 ± 1.5 ppm, paired t= -7.7 $P < 0.001$ vs. pre-abstinence).

Multiplanar rapidly acquired gradient-echo (MP-RAGE) structural images and gradient echo echo-planar images (TR = 2 sec, TE = 30 msec, matrix = 64 x 64, flip angle = 75, slices = 30, resolution = 3.5 mm isotropic with 0 gap) were acquired with a Siemens Trio 3 Tesla scanner and a circularly polarized (CP) head coil.

During scanning, subjects viewed smoking-related or neutral images (Gilbert and Rabinovich, Intl. Smoking Image Series v.1.2, 1999) or target images. Sixty smoking-related images, 60 neutral images, and 15 target images were presented in a pseudorandom order, with no more than 2 of the same stimulus type appearing consecutively. To eliminate practice effects, subjects viewed different images during their second scan.

Brain Voyager QX 1.10.2 (Brain Innovation, Maastricht, The Netherlands) was used to analyze data. Images were slice-time corrected, motion corrected, spatially smoothed using a 6mm Gaussian kernel, and spatially normalized into Talairach space. Large motion-related variability was modeled out for data points with motion >1.75mm (½ voxel).

A random effects general linear model (GLM) was run to compare BOLD activation in response to smoking versus neutral images between subjects, both before and during abstinence. To compare within subjects (abstinent vs pre-abstinent), a fixed effects general linear model was run. Contrast maps (smoking > neutral images) were created for each visit. Maps then were used to run a random effects ANOVA contrast (abstinent > pre-abstinent smokers). A Monte Carlo analysis was used to correct for multiple comparisons p > 0.01.

**Results:** At pre-abstinence, smoking-related cues induced positive BOLD responses ($z \geq 3.06$, $P < 0.01$) in frontal cortex (BA 8,9,10), anterior cingulate (BA 24,32), posterior cingulate (BA 29, 30, 31), temporal cortex (BA 21), occipital cortex (BA 18,19) and globus pallidus (fig. 1 middle row). During abstinence, smoking-related cues induced positive BOLD responses ($z \geq 3.06$, $P < 0.01$) in frontal cortex (BA 6, 8, 9, 10, 44, 47), anterior cingulate (BA 24 & 32), posterior cingulate (BA 23 & 31), paracentral lobule (BA 5), parahippocampal gyrus (BA 36), Transverses temporal gyrus (BA 41), pre- and postcentral gyrus (BA 1,2,3, & 4) and insula (BA 13). Subcortical positive BOLD responses were found in the thalamus, substantia nigra, caudate and putamen (fig. 1 bottom row). The contrast comparing pre-abstinence to abstinence revealed increased BOLD responses ($z \geq 3.06$, $P < 0.01$) in frontal cortex (primary motor BA 4) caudal anterior cingulate cortex (BA 24), posterior cingulate cortex (BA 23 & 31), insula (BA 13), thalamus, caudate nucleus, putamen, and substantia nigra (fig. 1 top row).

**Discussion:** The neuroanatomical distribution of positive BOLD responses is comparable to those previously reported in smoking-related and other drug-cue related functional imaging studies. Our findings also suggest that during abstinence on NRT, smoking-related cues induce positive BOLD responses in areas not detected in pre-abstinent subjects. Dorsal striatal and substantia nigra activations are particularly intriguing since the nigrostriatal circuit is known to participate in reinstatement of drug seeking during abstinence (Fuchs et al., 2006; See et al., 2007). The findings suggest that modulating the nigrostriatal circuit could help to reduce cue-induced brain activations and craving, and improve smoking cessation relapse rates.

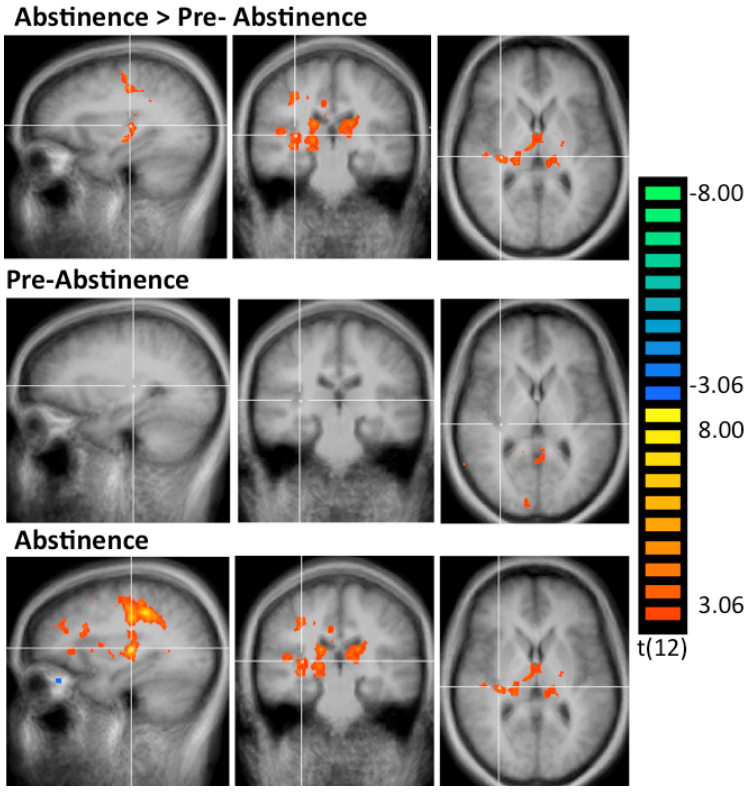


**Figure 1**: Functional MRI Results. Top row: Regional activity is significantly enhanced in abstinence versus pre-abstinence in the putamen, primary motor cortex, cingulate cortex, insula, thalamus, caudate nucleus, and substantia nigra (not shown). Cross hairs are located in right putamen for all images (Talairach coordinates: (x, y, z) 30, -23, 6). Middle row: During pre-abstinence, increased activity was not detected in the putamen in response to smoking-related images. Bottom row: During abstinence, smoking-related images increased activity in the putamen, frontal cortex, primary motor cortex, cingulate cortex, insula, caudate nucleus and thalamus. For all tests: t ≥ 3.06, corrected p < 0.001

**References:**

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