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Anterior insula activation during inhibition to smoking cues is associated with ability to maintain tobacco abstinence

Jodi M. Gilman[a,b,c,*], Milena Radoman[a], Randi M. Schuster[a,c], Gladys Pachas[a], Nour Azzouz[a], Maurizio Fava[a,c], A. Eden Evins[a,c]

[a] Massachusetts General Hospital (MGH), Department of Psychiatry, Boston, MA, USA
[b] Athinoula A. Martinos Center in Biomedical Imaging, Department of Radiology, MGH, Charlestown, MA, USA
[c] Harvard Medical School, Boston, MA, USA

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ABSTRACT

Relapse to smoking after initial abstinence is a major clinical challenge with significant public health consequences. At the brain and behavioral level, those who relapse to tobacco smoking have both greater cue-reactivity and lower inhibitory control than those who remain abstinent. Little is known about neural activation during inhibitory control tasks in the presence of drug-related cues. In the current study, tobacco smokers (SMK; n = 22) and non-smoking controls (CON; n = 19) completed a Go/NoGo task involving smoking cues during a functional magnetic resonance imaging (fMRI) scan. Following the scan session, smokers were required to quit smoking, and maintenance of abstinence was evaluated as part of a 12-week smoking cessation trial. We evaluated pre-cessation brain activity during NoGo trials in smokers who were versus were not able to quit smoking. We then compared fMRI and inhibitory control measures between smokers and non-smokers. We did not find differences between SMK and CON in performance or activation to smoking or neutral cues. However, compared to SMK who relapsed, SMK who attained biochemically-validated abstinence at the end of the smoking cessation trial had greater neural activation in the anterior insula during NoGo trials specifically with smoking-related cues. Results indicate that within SMK, decreased inhibitory control activation during direct exposure to drug-related stimuli may be a marker of difficulty quitting and relapse vulnerability.

1. Introduction

Several models highlight the role of impaired inhibitory control in the development and maintenance of addiction. The 'Inhibitory Control Dysfunction' theory states that response inhibition, defined as the ability to adaptively suppress behavior (Groman, James, & Jentsch, 2009), is impaired in those who are addicted. The 'Incentive Salience' theory of addiction (Berridge & Robinson, 1998) states that with repeated exposure to drugs, neural systems become sensitized to certain drug-related stimuli, which become 'salient' or 'attention-grabbing' to the user. These theories are complementary, in that poor response inhibition is often associated with difficulty resisting the desire to consume a substance, especially when exposed to highly salient substance-related cues (Dawe, Gullo, & Loxton, 2004).

Few studies have evaluated neural activation during inhibitory control tasks in the presence of drug-related cues (Froeliger et al., 2017; Goldstein et al., 2007; van Holst et al., 2012). A recent report in two cohorts of smokers found that greater activation in inhibitory control circuitry (e.g. right inferior frontal gyrus) was associated with quicker relapse to smoking (Froeliger et al., 2017), indicating that the investigation of neural response to inhibition may be a potential marker to determine whether a patient is likely to attain long-term abstinence. We designed and administered a smoking-related Go/NoGo task to be administered during functional magnetic resonance imaging (fMRI), to investigate the neural mechanisms underlying inhibitory control during exposure to smoking cues. Participants were instructed to respond as quickly as possible to frequently occurring 'Go' stimuli, and inhibit responses to infrequent 'NoGo' stimuli. Variants of this task have been widely used in neuroimaging studies, and a distributed network of regions underlying response inhibition, including the supplementary motor area (SMA) (Humberstone et al., 1997; Kawashima et al., 1996; Smith et al., 1998), dorsal and ventral frontal regions including the inferior frontal gyrus (IFG) (Casey et al., 1997; Kawashima et al., 1996; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Smith et al., 1998; Tsujimoto et al., 1997), anterior cingulate (ACC) and insula (Casey et al., 1997; Casey, Trainor, Orendi, & Schubert, 1996; Ponesse,

* Corresponding author at: MGH Center for Addiction Medicine, 60 Staniford St., Boston, MA 02114, USA.
E-mail address: jgilman1@partners.org (J.M. Gilman).

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1998; Smith et al., 1998), has been identified. Many of these same regions underlie craving and addictive behaviors (Everitt & Robbins, 2005; Goldstein et al., 2007; Goldstein & Volkow, 2002; Grant et al., 1996; Lee, Lim, Wiederhold, & Graham, 2005).

We investigated inhibitory control in the presence of smoking-related cues in tobacco smokers before they quit smoking and attempted to remain abstinent as well as in matched non-smoking controls. We aimed to determine whether brain activation during inhibition to smoking or neutral cues was associated with relapse to smoking, and to discover differences between smokers and non-smokers in brain activation when asked to inhibit a response to cues. As relapse vulnerability is influenced by smoking-cue reactivity (Janes et al., 2010), understanding neurobiological mechanisms underlying inhibitory control to smoking cues could inform mechanisms underlying risk of relapse.

2. Methods

This study was approved by Partners Human Subjects Committee. All participants completed consent procedures prior to initiation of study procedures and were compensated for their time.

2.1. Participants

Twenty-two otherwise healthy nicotine-dependent smokers (SMK) were enrolled and evaluated prior to initiating a smoking cessation attempt as a part of a smoking cessation clinical trial (MGH; NCT01480232, PI: Evins and Fava). SMK met DSM-IV criteria for current nicotine dependence, reported smoking at least 5 cigarettes per day, and had a urine cotinine ≥30 ng/mL at baseline. Nineteen non-smoking controls (CON) were also enrolled. Potential participants with a substance-use disorder other than nicotine, positive ten-panel urine screen for recent use of illicit drugs (Medimpex United Inc.), current major depression, lifetime bipolar disorder or schizophrenia, or positive pregnancy test were excluded.

2.2. Assessments

SMK were permitted to smoke prior to fMRI scan. Baseline smoking was characterized with expired carbon monoxide (CO) and urine cotinine concentration, pack-years of tobacco smoking and cigarettes per day in the seven days prior to baseline, severity of nicotine dependence (Fagerstrom Test for Cigarette Dependence; FTND) (Heatherton, KL, Frecker, & Fagerström, 1991), and craving (Tiffany Questionnaire of Smoking Urges; TQSU) (Sanderson Cox STTL, 2001). Participants also completed the six-item Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes & Hatsukami, 1986). Based on smoking status at the end of the 12-week trial, SMK were characterized as abstinent based on the following criteria: Self-report of 2-week abstinence using Timeline Follow-Back (Harris et al., 2009), CO < 10 ppm, and cotinine < 50 ng/mL.

2.3. Go/No-Go paradigm design and behavioral analysis

Inhibitory control was assessed using a smoking-related Go/NoGo task, administered during an fMRI scan session, during which participants were presented with smoking or neutral images (Okuyemi et al., 2006) (see Fig. 1). A single trial consisted of a stimulus presented for 900 ms, followed by an inter-stimulus interval (ISI) of 100 ms. Participants were instructed to press a button on a keypad as quickly as possible every time they saw a different image (Go trial). If the image was the same as the preceding one, participants were asked not to press the button (NoGo trial). In total, the task took 15 min and 12 s (over two runs) to complete and was comprised of 800 trials (400 smoking and 400 neutral), presented in random order. Twenty trials (5%) in each run were NoGo trials. The task was practiced at least once outside and inside the scanner or until a participant reached 100% accuracy. Accuracy (correct hits and correct inhibitions), and reactions times for hits were recorded.

2.4. Acquisition and analysis of neuroimaging data

Participants were scanned using a 3 T Siemens (Erlangen, Germany) Skyra scanner with a 32-channel head coil at the Martinos Center for Biomedical Imaging. Whole-brain T1-weighted 1 mm isotropic structural scans were collected using a 3D multiecho MPRAGE sequence (176 sagittal slices, 256 mm FoV, TR 2530 ms, TI 1200 ms, 2× GRAPPA acceleration, TE 1.64/3.5/5.36/7.22 ms, BW 651 Hz/px, T_{acq} 6:03 min) (van der Kouwe, Benner, Salat, & Fischl, 2008). Functional scans were collected using a 2D gradient echo EPI sequence (31 slices, 3 mm thick, 0.6 mm gap, 216 mm FoV, 3 mm^2 in-plane resolution, TR 2 s, TE 30 ms, BW 2240 Hz/px). All acquisitions were automatically positioned using AutoAlign (van der Kouwe et al., 2005). fMRI data processing was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of the FSL fMRI processing stream (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Each participant's functional and structural scans were registered using FSL's linear registration tool (FLIRT), and then these scans were registered to standard space images using both FLIRT and FSL's nonlinear registration tool (FNIRT) (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001). Standard pre-processing was applied. Higher-level group analysis was carried out using FSL's non-parametric permutation method (FSL Randomise; Winkler, Ridgway, Webster, Smith, & Nichols, 2014) with cluster-based thresholding corrected for multiple comparisons using a cluster forming threshold of z = 2.3 and a family-wise error corrected threshold of p < .05. For all analyses, we used an anatomically defined ROI mask comprised of the bilateral insula, IFG, dorsolateral prefrontal cortex (DLPFC), dorsal medial PFC (DMPFC), orbitofrontal cortex, medial prefrontal cortex (MPFC), striatum (nucleus accumbens, putamen, caudate), thalamus, and amygdala (see Froeliger et al., 2017; Janes et al., 2017a). The groups were compared on two primary contrasts: inhibit trials for neutral images, and inhibit trials for smoking images. Neutral and Smoking inhibit trials were also directly contrasted.

2.5. Region-of-interest (ROI) analyses: relation to smoking relapse

Beta weights for the smoking versus neutral image contrasts were extracted from anatomical ROIs consisting of the (1) anterior insula, and (2) right IFG, chosen a priori based on regions previously implicated in inhibitory control and addiction (Feltenstein & See, 2008; Garavan, Ross, & Stein, 1999; Koob & Volkow, 2010). All masks were parcellated using validated landmarks (Gasic et al., 2009; Perlis et al., 2008). Activation signal was extracted from each participant using the FSL program, featquery (http://fsl.fmrib.ox.ac.uk/fsl/fsl4.0/feat5/featquery.html). A linear regression controlling for FTND score was calculated to evaluate whether fMRI signal in the anterior insula or right IFG could predict whether smokers would relapse or remain abstinent in the parent clinical trial.

3. Results

3.1. Participants

See Table 1 for participants' baseline demographic and clinical information. SMK and CON did not differ on basic demographic measures (sex, age, education). Additionally, SMK who relapsed (n = 12) and those who remained abstinent (n = 10) did not differ on baseline smoking-related measures (expired CO, cigarettes smoked per day, pack years, nicotine dependence, craving and withdrawal).

3.2. Behavioral results

Across both CON and SMK, there was a main effect of Condition on response accuracy (F = 103.7, p < .001); participants made more