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

Citation	Gilman, Jodi M., Milena Radoman, Randi M. Schuster, Gladys Pachas, Nour Azzouz, Maurizio Fava, and A. Eden Evins. 2018. "Anterior insula activation during inhibition to smoking cues is associated with ability to maintain tobacco abstinence." Addictive Behaviors Reports 7 (1): 40-46. doi:10.1016/j.abrep.2018.01.002. http://dx.doi.org/10.1016/j.abrep.2018.01.002.
Published Version	doi:10.1016/j.abrep.2018.01.002
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:35014377
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

Addictive Behaviors Reports 7 (2018) 40–46

Contents lists available at ScienceDirect

Addictive Behaviors Reports

journal homepage: www.elsevier.com/locate/abrep

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

ARTICLE INFO

Keywords:
Smoking cessation
Tobacco
fMRI
Insula
Cue
Relapse
Anterior cingulate cortex
ACC

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).

https://doi.org/10.1016/j.abrep.2018.01.002
Received 28 September 2017; Received in revised form 5 January 2018; Accepted 7 January 2018
Available online 09 January 2018

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

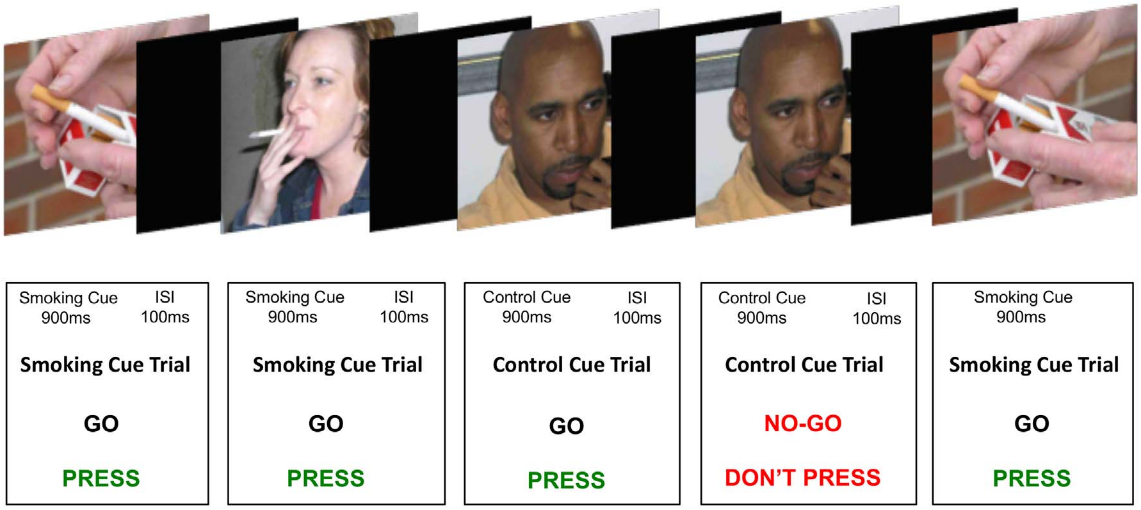

Fig. 1. Go/NoGo task. Participants were presented with a set of visual cues with smoking or control content. Participants were instructed to press a button on a keypad as quickly as possible each time they saw a new image (GO trial). Participants were asked not to press any button when the image presented was identical to the preceding image (NO-GO trial). Two separate runs of this task were completed.

errors on NoGo versus Go trials (Fig. 2A). There were no main effects of Stimulus (smoking: M = 0.59, SD = 0.05, neutral: M = 0.55, SD = 0.01, p = .73) or Group on response accuracy (SMK: M = 0.76, SD = 0.24, CON: M = 0.76, SD = 0.21; p = .78). There was a main effect of stimulus type on reaction time, F = 7.05, p = .01, indicating that participants generally responded faster to smoking-related Go trials than to neutral Go trials (Fig. 2B). No other significant effects were found for reaction times. No significant correlations were found between Go-NoGo behavioral measures (i.e., accuracy and reaction time) and smoking-related measures (e.g. FTND scores or end-of-treatment abstinence) (all p-values > .10).

3.3. Neuroimaging results

After correcting for multiple comparisons using FSL's non-parametric permutation method (Winkler et al., 2014), there were no regions that showed suprathreshold differences between smoking at neutral cues in either SMK or CON. For activation observed from the contrast of NoGo > Baseline trials in smoking and neutral trials, see Table 2 and Fig. 3.

3.3.1. NoGo activation to neutral cues

In NoGo trials presenting neutral cues, CON and SMK showed activation in the bilateral orbitofrontal cortex and bilateral insula. SMK also showed significant activation in the right IFG. There were no regions that showed significant differences between SMK and CON.

3.3.2. NoGo activation to smoking cues

In NoGo trials presenting smoking cues, CON and SMK both showed activation in the right IFG. SMK also showed activation in the left middle frontal gyrus and left nucleus accumbens. There were no regions that showed significant differences between SMK and CON. When we compared smoking to neutral images during NoGo trials, there were no differences in the contrast of smoking vs neutral images in either group.

3.3.3. Association between brain activation during NoGo trials and relapse to smoking

3.3.3.1. Anterior insula. Among SMK, after controlling for FTND scores, those who maintained abstinence had greater activation during NoGo smoking trials in both the left (β = −0.41, t = −2.27, p = .03), and the right (β = −0.51, t = −2.50, p = .02) anterior insula (Fig. 4). FTND scores were associated with activation in the left anterior insula (β = −0.44, t = −2.42, p = .03) but not the right anterior insula activation (β = −0.11, t = −0.54, p = .59). Activation to neutral images in NoGo trials was not different between SMK who did and did not relapse to smoking, and was not associated with FTND (p-

Table 1
Characteristics of participants.

	Controls (n = 19)	Smokers (n = 22)		p value
		Abstinent (n = 10)	Relapse (n = 12)	
Sex (M/F)	9/10	8/2	8/4	N/A
Age (years)	39.63 (12.41)	35.00 (11.29)	42.25 (11.51)	0.15
Education (years)	15.68 (2.26)	13.90 (1.66)	14.83 (1.80)	0.22
WASI-II Vocabulary T Score	58.95 (12.59)	52.10 (6.42)	53.42 (8.06)	0.72
WASI-II Matrix Reasoning T Score	53.84 (14.26)	52.80 (12.71)	53.83 (8.12)	0.96
Expired CO (ppm) at baseline	2.26 (1.19)	15.80 (11.79)	25.92 (14.81)	0.10
Cigarettes/day at baseline	–	15.85 (7.66)	21.46 (11.79)	0.21
Pack years	–	17.30 (10.44)	23.92 (11.75)	0.18
FTND scores at baseline	–	4.40 (1.90)	6.00 (2.83)	0.14
Age of daily smoking onset (years)	–	15.50 (2.72)	17.17 (2.25)	0.13
Total craving score (TQSU)	–	39.30 (14.72)	37.75 (11.26)	0.78
Withdrawal score (MNWS)	–	4.60 (2.95)	3.75 (2.49)	0.47

Abbreviations: (F) female; (M) male; (WASI), Wechsler Abbreviated Scale of Intelligence, 2nd Edition; (CESD), Center for Epidemiological Studies-Depression; (CO), carbon monoxide; (FTND), Fagerstrom Test for Nicotine Dependence; (TQSU), Tiffany Questionnaire of Smoking Urges; (MNWS), Minnesota Nicotine Withdrawal Scale.
Data are presented as mean values (SD in parentheses).

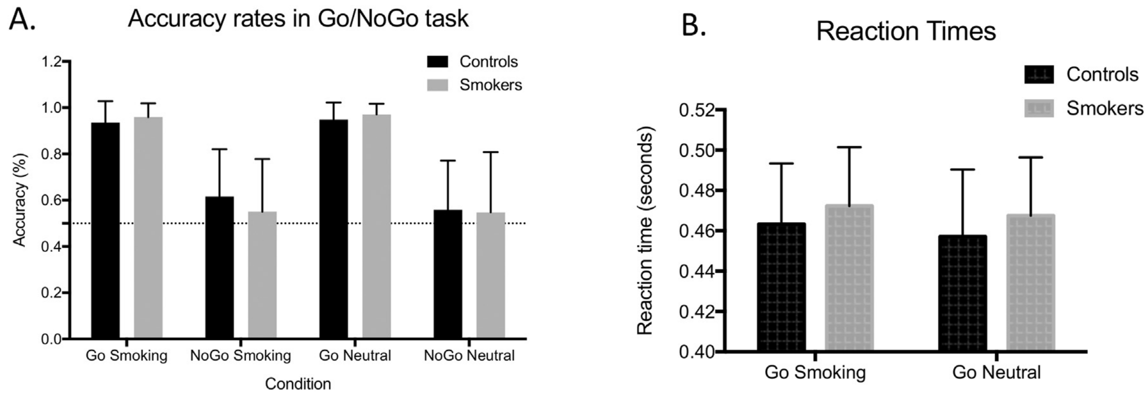

Fig. 2. A. Accuracy during the Go/NoGo task. There was a robust main effect of response type, $F = 103.7$, $p < .001$ showing that participants were less accurate when asked to inhibit their response (NoGo trials). Overall task performance was not different in smokers and controls. There were also no main or interaction effects of stimulus type (smoking or neutral) on accuracy of responding. B. There was a main effect of stimulus type on reaction time, indicating that participants generally responded faster to smoking-related Go trials than to neutral Go trials. No other significant effects were found for reaction times.

Table 2
Activation during NoGo trials on Go-No/Go task.

HEM	Region	x	y	z	Voxels	p value
Neutral images						
Controls						
Left	Frontal orbital cortex, insular cortex	−28	20	−12	772	0.008
Right	Frontal orbital cortex, insular cortex	32	22	−16	762	0.009
Smokers						
Right	Inferior frontal gyrus	52	14	18	657	0.008
Left	Frontal orbital cortex, insular cortex	−30	16	−14	610	0.015
Right	Frontal orbital cortex, insular cortex	40	20	−14	517	0.042
Smoking images						
Controls						
Right	Frontal pole, inferior frontal gyrus	46	36	14	433	0.021
Smokers						
Right	Inferior frontal gyrus	48	18	18	803	0.001
Left	Middle frontal gyrus	−44	36	20	658	0.023
Left	Nucleus accumbens	−16	10	−6	622	0.027

p values generated using FSL's non-parametric permutation method (Randomise) 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 $p < .05$. All analyses used an anatomically defined ROI mask comprised of the bilateral insula, IFG, orbitofrontal cortex, MPFC, DLPFC, DMPFC, striatum (nucleus accumbens, putamen, caudate), thalamus, and amygdala.

values > .10).

3.3.3.2. Right IFG. Among SMK, end-of-study abstinence was not associated with activation of the right IFG during NoGo smoking trials ($\beta = -0.78$, $t = -0.36$, $p = .75$). FTND scores also did not predict activation of the right IFG ($\beta = -0.11$, $t = -0.54$, $p = .59$). Inhibitory control activation to neutral images also was not associated with abstinence or with FTND (p-values > .10).

4. Discussion

Though poor response inhibition in individuals with substance use disorder is associated with difficulties resisting the urge to use a substance, especially when exposed to highly salient substance-related cues (Dawe et al., 2004), few studies have directly investigated the interaction between inhibitory control and cue reactivity. In the current study, although both smokers and controls showed expected activation in inhibitory control regions during exposure to neutral and smoking cues, we did not find significant differences between the smoking and control groups, and smoking vs neutral images did not yield significant differences in activation in either group. However, we found activation in the insula during inhibition to smoking cues to be associated with likelihood of relapsing during 12 weeks of smoking cessation treatment. Decreased activation in the anterior insula during inhibitory control in the presence of smoking-related cues may reflect potentiated relapse vulnerability.

The insula has been consistently implicated in addictive behaviors. The anterior insula in particular has emerged as a critical node in circuitry related to maintenance of tobacco addiction, as insula activity has been consistently associated with cigarette craving (Brody et al., 2007). In a similar cohort (NCT01480232), altered anterior insular reactivity during passive viewing of smoking cues was predictive of relapse (Janes et al., 2017b).

We suggest that less activation in the anterior insula during inhibition, particularly in the face of highly salient cues may underlie impaired inhibitory control related to smoking behaviors. Smokers who relapsed had less activation in the bilateral anterior insula, even after adjusting for severity of nicotine dependence using the FTND scale. In contrast, the right IFG, which is a critical region in inhibitory control (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003) but not often implicated in nicotine addiction, did not show differential activation between those who relapsed and those who remained abstinent.

We did not observe performance differences between smokers and non-smokers with respect to accuracy or reaction time to either neutral or smoking cues. Previous studies in smokers report mixed findings; while some show no differences in inhibitory control behavior between smokers and non-smokers (Dinn, Aycicegi, & Harris, 2004; Reynolds et al., 2007), others have reported correlations between lower behavioral inhibition and higher cigarette consumption (Galvan, Poldrack, Baker, McGlennen, & London, 2011; Glass et al., 2009; McClernon, Kozink, & Rose, 2008). As with behavioral differences, there is a lack of consensus on whether differences in neural activation during inhibition between SMK and CON exist. Though some studies report hypoactivation in smokers, particularly in the ACC, IFG, and the dorsolateral prefrontal cortex (de Ruiter, Oosterlaan, Veltman, van den Brink, & Goudriaan, 2012; Goldstein & Volkow, 2011; Luijten et al., 2014), others have reported no group differences (Galvan et al., 2011). Larger studies with standardized experimental designs may be able to better determine the extent to which brain activity underlying inhibition is impaired in smokers compared to controls.

It is important to note that unlike many previous cue-reactivity studies (Balter, Good, & Barrett, 2015; McClernon et al., 2008; McClernon, Kozink, Lutz, & Rose, 2009; Owens et al., 2017), we did not observe significant differences in brain regions between smoking and

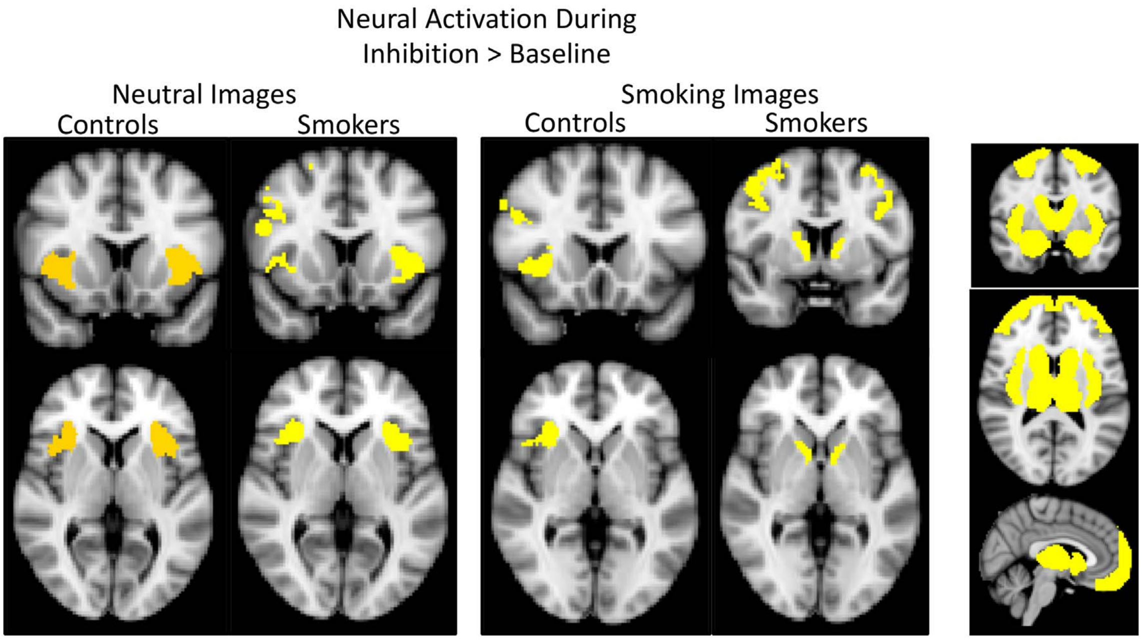

Fig. 3. Neural activation during NoGo > baseline in controls and smokers. Direct comparisons revealed no significant differences between brain activation during response inhibition to smoking vs neutral images in smokers or non-smokers. Significant results from NoGo trials were thresholded using FSL's non-parametric permutation method (FSL Randomise; Winkler et al., 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 $p < .05$. All analyses used an anatomically defined ROI mask comprised of the bilateral insula, orbitofrontal cortex, IFG, MPFC, DLPFC, DMPFC striatum (nucleus accumbens, putamen, caudate), thalamus, and amygdala (shown on right side of figure).

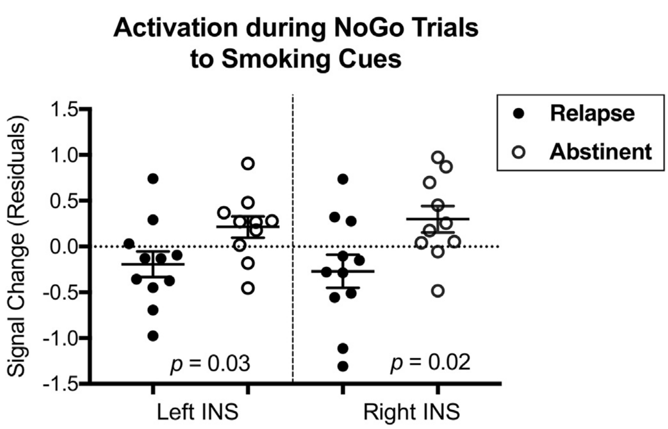

Fig. 4. Neural activation during inhibitory control to smoking cues by subsequent abstinence status (abstinence vs relapsed). SMK who relapsed had significantly less activation in the anterior insula during inhibitory control to smoking cues than those who stayed quit.

neutral trials in either SMK or CON. There are at least three possible explanations for this negative finding. First, the correction method used in this paper is stricter than that used in many fMRI reports that have shown these differences, and it is possible that previously significant results in the literature would not have held up under nonparametric corrections (see Eklund, Nichols, & Knutsson, 2016 of full explanation). Second, it is now well-known that not all smokers are cue-reactive; many factors, including self-reported nicotine dependence, prescan withdrawal symptoms (craving and negative affect), gender effects (McClernon et al., 2008), and even nicotine metabolism (Falcone et al., 2016), can influence who is cue-reactive and who is not among smokers. In a small sample size of 22 smokers, it is possible that not all participants were cue-reactive, obscuring a significant finding. Finally, it is possible that the smoking cues in this study were not appetitive enough to elicit a significant brain response.

There are methodological limitations to the study. In our Go/NoGo version, only 5% of stimuli were NoGo, which resulted in high error rates in both groups during the task on NoGo trials. We designed the task in this way to increase its difficulty and therefore maximize any potential differences between SMK and CON. However, even with this difficult version, behavioral inhibitory control on the Go/NoGo is likely quite different than the behavioral control needed to abstain from smoking in the real world. Furthermore, this limited number of NoGo trials may have contribute to a lack of power to observe significant findings.

In conclusion, results from the current study suggest that, while brain activation during inhibition to smoking cues does not significantly differ from inhibition to neutral cues, decreased activation in the anterior insula to inhibition of smoking cues may be associated with relapse among smokers attempting to remain abstinent.

Disclosures

Financial Disclosures: A. Eden Evins received research grant funding and/or study supplies to her institution from Forum Pharmaceuticals, GSK, and Pfizer, and has performed consulting work for Reckitt Benckiser and Pfizer. M. Fava was a consultant to Forum Pharmaceuticals and Envivo Pharmaceuticals. For a complete list of lifetime disclosures for M. Maurizio Fava, please see http://mghcme.org/faculty/faculty-detail/maurizio_fava. No conflict declared for J. Gilman, M. Radoman, R. Schuster, N. Azzouz, or G. Pachas.

Funding

This work was supported by NIDA K01 DA034093 (JMG), NIDA R01 DA030992 (AEE, MF), NIDA R01 DA04204 (JMG) and NIDA K24 DA030443 (AEE). These funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

Conceived and designed the experiments: JMG, AEE, MF. Performed the experiments: MR JMG. Oversaw clinical aspects: GP, Analyzed the data: JMG MR. Wrote the paper: JMG, MR, NA, RS. All authors have approved the final article.

References

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience, 6*(2), 115–116. http://dx.doi.org/10.1038/nn1003 (PubMed PMID: 12536210).

Balter, L. J., Good, K. P., & Barrett, S. P. (2015). Smoking cue reactivity in current smokers, former smokers and never smokers. *Addictive Behaviors, 45*, 26–29. http://dx.doi.org/10.1016/j.addbeh.2015.01.010 (PubMed PMID: 25635692).

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews, 28*(3), 309–369 (PubMed PMID: 9858756).

Brody, A. L., Mandelkern, M. A., Olmstead, R. E., Jou, J., Tiongson, E., Allen, V., et al. (2007). Neural substrates of resisting craving during cigarette cue exposure. *Biological Psychiatry, 62*(6), 642–651.

Casey, B., Trainor, R., Orendi, J., & Schubert, A. (1996). A functional magnetic resonance imaging (fMRI) study of ventral prefrontal cortex mediation of response inhibition. *Proc Soc Neurol. 22*, 1107.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., et al. (1997). A developmental functional MRI study of prefrontal activation during performance of a Go-No-Go task. *Journal of Cognitive Neuroscience, 9*(6), 835–847. Epub 1997/11/01 https://doi.org/10.1162/jocn.1997.9.6.835 (PubMed PMID: 23964603) .

Dawe, S., Gullo, M. J., & Loxton, N. J. (2004). Reward drive and rash impulsiveness as dimensions of impulsivity: Implications for substance misuse. *Addictive Behaviors, 29*(7), 1389–1405. Epub 2004/09/04 https://doi.org/10.1016/j.addbeh.2004.06.004 (S0306460304002187 [pii]. PubMed PMID: 15345272) .

Dinn, W. M., Aycicegi, A., & Harris, C. L. (2004). Cigarette smoking in a student sample: Neurocognitive and clinical correlates. *Addictive Behaviors, 29*(1), 107–126. http://dx.doi.org/10.1016/j.addbeh.2003.07.001.

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences of the United States of America, 113*(28), 7900–7905. http://dx.doi.org/10.1073/pnas.1602413113 (PubMed PMID: 27357684; PubMed Central PMCID: PMCPMC4948312).

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: From actions to habits to compulsion. *Nature Neuroscience, 8*(11), 1481–1489.

Falcone, M., Cao, W., Bernardo, L., Tyndale, R. F., Loughead, J., & Lerman, C. (2016). Brain responses to smoking cues differ based on nicotine metabolism rate. *Biological Psychiatry, 80*(3), 190–197. http://dx.doi.org/10.1016/j.biopsych.2015.11.015 (PubMed PMID: 26805583; PubMed Central PMCID: PMCPMC5625335).

Feltenstein, M. W., & See, R. E. (2008). The neurocircuitry of addiction: An overview. *British Journal of Pharmacology, 154*(2), 261–274. http://dx.doi.org/10.1038/bjp.2008.51 (PubMed PMID: 18311189; PubMed Central PMCID: PMCPMC2442446).

Froeliger, B., McConnell, P. A., Bell, S., Sweitzer, M., Kozink, R. V., Eichberg, C., et al. (2017). Association between baseline corticothalamic-mediated inhibitory control and smoking relapse vulnerability. *JAMA Psychiatry, 74*(4), 379–386. http://dx.doi.org/10.1001/jamapsychiatry.2017.0017 (PubMed PMID: 28249070; PubMed Central PMCID: PMCPMC5562280).

Galvan, A., Poldrack, R. A., Baker, C. M., McGlennen, K. M., & London, E. D. (2011). Neural correlates of response inhibition and cigarette smoking in late adolescence. *Neuropsychopharmacology, 36*(5), 970–978. http://dx.doi.org/10.1038/npp.2010.235 (PubMed PMID: 21270772).

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proceedings of the National Academy of Sciences of the United States of America, 96*(14), 8301–8306 (PubMed PMID: 10393989; PubMed Central PMCID: PMCPMC22229).

Gasic, G. P., Smoller, J. W., Perlis, R. H., Sun, M., Lee, S., Kim, B. W., et al. (2009). BDNF, relative preference, and reward circuitry responses to emotional communication. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 150B*(6), 762–781. Epub 2009/04/24 https://doi.org/10.1002/ajmg.b.30944 (PubMed PMID: 19388013) .

Glass, J. M., Buu, A., Adams, K. M., Nigg, J. T., Puttler, L. I., Jester, J. M., et al. (2009). Effects of alcoholism severity and smoking on executive neurocognitive function. *Addiction, 104*(1), 38–48. http://dx.doi.org/10.1111/j.1360-0443.2008.02415.x (PubMed PMID: 19133887).

Goldstein, R. Z., Tomasi, D., Rajaram, S., Cottone, L. A., Zhang, L., Te, M., et al. (2007). Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience, 144*(4), 1153–1159.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *The American Journal of Psychiatry, 159*(10), 1642–1652 (PubMed PMID: PMC1201373).

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*(11), 652–669.

Grant, S., London, E. D., Newlin, D. B., Villemagne, V. L., Liu, X., Contoreggi, C., et al. (1996). Activation of memory circuits during cue-elicited cocaine craving. *Proceedings of the National Academy of Sciences, 93*(21), 12040–12045.

Groman, S. M., James, A. S., & Jentsch, J. D. (2009). Poor response inhibition: At the nexus between substance abuse and attention deficit/hyperactivity disorder. *Neuroscience and Biobehavioral Reviews, 33*(5), 690–698. Epub 2008/09/16 https://doi.org/10.1016/j.neubiorev.2008.08.008 S0149-7634(08)00139-5 [pii]. (PubMed PMID: 18789354; PubMed Central PMCID: PMC2728075) .

Harris, K. J., Golbeck, A. L., Cronk, N. J., Catley, D., Conway, K., & Williams, K. B. (2009). Timeline follow-back versus global self-reports of tobacco smoking: A comparison of findings with nondaily smokers. *Psychology of Addictive Behaviors, 23*(2), 368–372. http://dx.doi.org/10.1037/a0015270 (PubMed PMID: 19586155; PubMed Central PMCID: PMCPMC2784668).

Heatherton, T. F., KL, Frecker, R. C., & Fagerström, K. O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction, 86*(9), 1119–1127.

van Holst, R. J., van der Meer, J. N., McLaren, D. G., van den Brink, W., Veltman, D. J., & Goudriaan, A. E. (2012). Interactions between affective and cognitive processing systems in problematic gamblers: A functional connectivity study. *PLoS One, 7*(11), e49923. http://dx.doi.org/10.1371/journal.pone.0049923 (PubMed PMID: 23209619; PubMed Central PMCID: PMCPMC3509135).

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry, 43*(3), 289–294 (PubMed PMID: 3954551).

Humberstone, M., Sawle, G. V., Clare, S., Hykin, J., Coxon, R., Bowtell, R., et al. (1997). Functional magnetic resonance imaging of single motor events reveals human presupplementary motor area. *Annals of Neurology, 42*(4), 632–637. http://dx.doi.org/10.1002/ana.410420414 (PubMed PMID: 9382475).

Janes, A. C., Gilman, J. M., Radoman, M., Pachas, G., Fava, M., & Evins, A. (2017a). Revisiting the role of the insula and smoking cue-reactivity in relapse: A replication and extension of neuroimaging findings. *Drug and Alcohol Dependence, 179*, 8–12. http://dx.doi.org/10.1016/j.drugalcdep.2017.06.012 (Epub 2017 Jul 12. PMID: 28735078).

Janes, A. C., Gilman, J. M., Radoman, M., Pachas, G., Fava, M., & Evins, A. E. (2017b). Revisiting the role of the insula and smoking cue-reactivity in relapse: A replication and extension of neuroimaging findings. *Drug and Alcohol Dependence, 179*, 8–12.

Janes, A. C., Pizzagalli, D. A., Richardt, S., de, B. F. B., Chuzi, S., Pachas, G., et al. (2010). Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biological Psychiatry, 67*(8), 722–729. http://dx.doi.org/10.1016/j.biopsych.2009.12.034 (PubMed PMID: 20172508).

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage, 17*(2), 825–841 (Epub 2002/10/16. PubMed PMID: 12377157).

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*(2), 143–156 (Epub 2001/08/23. PubMed PMID: 11516708).

Kawashima, R., Satoh, K., Itoh, H., Ono, S., Furumoto, S., Gotoh, R., et al. (1996). Functional anatomy of GO/NO-GO discrimination and response selection—A PET study in man. *Brain Research, 728*(1), 79–89 (Epub 1996/07/22. PubMed PMID: 8864300).

Konishi, S., Nakajima, K., Uchida, I., Sekihara, K., & Miyashita, Y. (1998). No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *The European Journal of Neuroscience, 10*(3), 1209–1213 (Epub 1998/09/30. PubMed PMID: 9753190).

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*(1), 217–238. http://dx.doi.org/10.1038/npp.2009.110 (PubMed PMID: 19710631; PubMed Central PMCID: PMCPMC2805560).

van der Kouwe, A. J., Benner, T., Fischl, B., Schmitt, F., Salat, D. H., Harder, M., et al. (2005). On-line automatic slice positioning for brain MR imaging. *NeuroImage, 27*(1), 222–230. Epub 2005/05/12 https://doi.org/10.1016/j.neuroimage.2005.03.035 (PubMed PMID: 15886023) .

van der Kouwe, A. J., Benner, T., Salat, D. H., & Fischl, B. (2008). Brain morphometry with multiecho MPRAGE. *NeuroImage, 40*(2), 559–569. Epub 2008/02/05 https://doi.org/10.1016/j.neuroimage.2007.12.025 (PubMed PMID: 18242102; PubMed Central PMCID: PMC2408694) .

Lee, J.-H., Lim, Y., Wiederhold, B. K., & Graham, S. J. (2005). A functional magnetic resonance imaging (FMRI) study of cue-induced smoking craving in virtual environments. *Applied Psychophysiology and Biofeedback, 30*(3), 195–204.

Luijten, M., Machielsen, M. W., Veltman, D. J., Hester, R., de Haan, L., & Franken, I. H. (2014). Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *Journal of Psychiatry & Neuroscience, 39*(3), 149–169. http://dx.doi.org/10.1503/jpn.130052 (PubMed PMID: 24359877).

McClernon, F. J., Kozink, R. V., Lutz, A. M., & Rose, J. E. (2009). 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology, 204*(1), 25–35. http://dx.doi.org/10.1007/s00213-008-1436-9 (PubMed PMID: 19107465; PubMed Central PMCID: PMCPMC2810714).

McClernon, F. J., Kozink, R. V., & Rose, J. E. (2008). Individual differences in nicotine dependence, withdrawal symptoms, and sex predict transient fMRI-BOLD responses to smoking cues. *Neuropsychopharmacology, 33*(9), 2148–2157. http://dx.doi.org/10.1038/sj.npp.1301618 (PubMed PMID: 17987060).

Okuyemi, K. S., Powell, J. N., Savage, C. R., Hall, S. B., Nollen, N., Holsen, L. M., et al. (2006). Enhanced cue-elicited brain activation in African American compared with Caucasian smokers: An fMRI study. *Addiction Biology, 11*(1), 97–106. http://dx.doi.org/10.1111/j.1369-1600.2006.00007.x (PubMed PMID: 16759342).

Owens, M. M., MacKillop, J., Gray, J. C., Beach, S. R. H., Stein, M. D., Niaura, R. S., et al. (2017). Neural correlates of tobacco cue reactivity predict duration to lapse and continuous abstinence in smoking cessation treatment. *Addiction Biology*. http://dx.doi.org/10.1111/adb.12549 (PubMed PMID: 28877410).

Perlis, R. H., Holt, D. J., Smoller, J. W., Blood, A. J., Lee, S., Kim, B. W., et al. (2008). Association of a polymorphism near CREB1 with differential aversion processing in the insula of healthy participants. *Archives of General Psychiatry, 65*(8), 882–892. Epub 2008/08/06. 65/8/882 [pii] https://doi.org/10.1001/archgenpsychiatry.

2008.3 (PubMed PMID: 18678793) .
Ponesse, J. (1998). Functional neuroimaging of the inhibition of a motor response. *NeuroImage, 7*, P-0972.
Reynolds, B., Patak, M., Shroff, P., Penfold, R. B., Melanko, S., & Duhig, A. M. (2007). Laboratory and self-report assessments of impulsive behavior in adolescent daily smokers and nonsmokers. *Experimental and Clinical Psychopharmacology, 15*(3), 264–271. http://dx.doi.org/10.1037/1064-1297.15.3.264 (PubMed PMID: 17563213).
de Ruiter, M. B., Oosterlaan, J., Veltman, D. J., van den Brink, W., & Goudriaan, A. E. (2012). Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug and Alcohol Dependence, 121*(1–2), 81–89. http://dx.doi.org/10.1016/j.drugalcdep.2011.08.010 (PubMed PMID: 21893386).
Sanderson Cox STTL (2001). Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & Tobacco Research, 3*(1), 7–16. http://dx.doi.org/10.1080/14622200124218.
Smith, A. M., Kiehl, K. A., Memdrek, A., Forster, B. B., Hare, R. D., & Liddle, P. F. (1998). Whole brain fMRI of a Go/No Go task. *NeuroImage, 7*.
Tsujimoto, T., Ogawa, M., Nishikawa, S., Tsukada, H., Kakiuchi, T., & Sasaki, K. (1997). Activation of the prefrontal, occipital and parietal cortices during go/no-go discrimination tasks in the monkey as revealed by positron emission tomography. *Neuroscience Letters, 224*(2), 111–114 (Epub 1997/03/14. PubMed PMID: 9086469).
Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage, 92*, 381–397. http://dx.doi.org/10.1016/j.neuroimage.2014.01.060 (PubMed PMID: 24530839; PubMed Central PMCID: PMCPMC4010955).