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Neural Basis of Smoking-Related Difficulties in Emotion Regulation

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Abstract

Background: Negative emotional states contribute to cigarette smoking, and difficulties in regulating these states can hinder smoking cessation. Understanding the neural bases of these difficulties in smokers may facilitate development of novel therapies for Tobacco Use Disorder.
Methods: Thirty-seven participants (18 smokers, 19 nonsmokers; 16–21 years old) completed the Difficulties in Emotion Regulation Scale (DERS), which is comprised of 6 subscales (lack of emotional clarity, lack of emotional awareness, limited access to emotion regulation strategies, nonacceptance of emotional responses, difficulties engaging in goal-directed behaviors, and impulse control difficulties) that combine to provide a total score. Participants also underwent functional magnetic resonance imaging to determine resting-state functional connectivity of the amygdala. Separate ANOVAs were used to determine group differences in self-reports on the DERS. Voxel-wise linear mixed models were performed to determine whether group influenced relationships between whole-brain functional connectivity of the amygdala and scores on the DERS.
Results: Compared with nonsmokers, smokers reported greater difficulties in emotion regulation, denoted by higher total scores on the DERS. Group differences were observed on a subscale of lack of emotional clarity, but no other subscale differences on the DERS were observed. Nonsmokers exhibited a greater negative correlation than smokers between lack of emotional clarity scores and connectivity of the amygdala with the left inferior frontal gyrus. Finally, this amygdala-to-left inferior frontal gyrus connectivity was weaker in smokers than in nonsmokers.
Conclusions: These findings suggest that difficulties in emotion regulation in smokers are at least partially due to lack of emotional clarity. Given the role of the inferior frontal gyrus in understanding emotional states, strengthening connectivity between the amygdala and the inferior frontal gyrus may improve emotional clarity to help smokers regulate their negative emotions, thereby improving their ability to quit smoking.

Key Words: Smoking, emotion regulation, fMRI, amygdala, inferior frontal gyrus

Introduction

Tobacco smoking is one of the leading causes of disease and death worldwide and contributes to an estimated 6 million deaths per year worldwide (Britton et al., 2017). Many smokers fail to quit because they are unable to tolerate abstinence-induced negative affect (Shiffman and Waters, 2004). In this regard, experimental induction of negative emotional states

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Significance Statement

This study extends previous observations that negative emotional states hinder smoking cessation by examining difficulties in emotion regulation in young smokers as well as determining the neural mechanisms of these difficulties. This is the first study to specifically show that smokers have greater difficulty in emotion regulation than nonsmokers and that this is at least partially due to a lack of emotional clarity. Further, our results reveal that this lack of emotional clarity is linked to weak connectivity of the amygdala with the left inferior frontal gyrus. Given the role of the inferior frontal gyrus in interoception, our results suggest that strengthening amygdala–inferior frontal gyrus connectivity may improve a smoker's emotional clarity, which may in turn improve their ability to regulate their negative emotions and thus successfully quit smoking.

increases cigarette craving in smokers who have been abstinent for approximately 6 hours (Juliano and Brandon, 2002), and increases in negative affect during abstinence promote relapse (Shiffman and Waters, 2004). Use of strategies to regulate negative emotions, particularly during a quit attempt, may therefore aid smoking cessation.

Emotion regulation refers to the use of cognitive strategies, such as reappraisal or attentional distraction, to modify the valence or intensity of an emotion (Gross et al., 1998). No previous study has specifically compared smokers and nonsmokers in their ability to use these strategies, but individuals with alcohol (Fox et al., 2008) and cocaine (Fox et al., 2007) use disorders have greater difficulties in emotion regulation compared with those who do not have drug use disorders. If smokers also experience these difficulties, improving their ability to regulate their negative emotions could facilitate smoking cessation. Notably, smokers who use reappraisal to regulate negative affect during a quit attempt are more able to refrain from smoking than those who do not (Beadman et al., 2015). Conversely, smokers who self-report greater difficulty in emotion regulation have a significantly higher likelihood of relapse during cessation than those with less difficulty (Farris et al., 2016).

The aforementioned studies of emotion regulation in individuals with substance use disorders (Fox et al., 2007, 2008; Farris et al., 2016) have used the Difficulty in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004), which is comprised of 6 subscales and provides a total score as well as 1 for each subscale. Farris et al (2016) reported only on the relationship between smoking relapse and the total DERS score, leaving open the question of which component score or scores are most prominent in Tobacco Use Disorder. Identifying specific aspects of emotion regulation that are especially problematic for smokers may help identify targets for smoking cessation therapies.

Understanding the neural mechanisms of smoking-related difficulties in emotion regulation may also aid cessation efforts. Buhle and Silvers et al (2014) conducted a meta-analysis of 34 studies in which participants were instructed to use reappraisal to downregulate cue-induced negative affect during functional magnetic resonance imaging (fMRI). Reappraisal consistently accompanied increased activation in the inferior frontal gyrus, middle frontal gyrus, dorsolateral and ventrolateral prefrontal cortices, bilateral anterior insula, left anterior cingulate cortex (ACC), left middle temporal gyrus, and superior parietal lobe but bilaterally decreased activity in the amygdala. In a subsequent psychophysiological interaction analysis, reappraisal success was positively correlated with functional connectivity between the amygdala and the inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, anterior insula, and ACC (Morawetz et al., 2017a). Furthermore, a recent meta-analysis of 93 studies examining the neural mechanisms of various emotion regulation strategies (reappraisal, suppression, attentional distraction, and controlled breathing) revealed that regardless of the strategy used, downregulation of negative affect consistently accompanied decreased activity in the bilateral amygdala and increased activity in the anterior insula, ventrolateral prefrontal cortex, inferior frontal gyrus, superior frontal gyrus, and supplementary motor area (Morawetz et al., 2017b). Although the brain regions involved in successful emotion regulation are well-established in healthy controls, the neural mechanisms of potential smoking-related difficulties in emotion regulation are unknown.

It is important to consider young smokers in cessation efforts. Emotion regulation abilities are still developing between the ages of 10 and 23 years (Silvers et al., 2012), while myelination and synaptic pruning in the frontal lobes continue into late adolescence (Giedd et al., 1999). Helping young smokers to quit may, therefore, allay the potential negative effects of smoking on brain and cognitive development. Further, because smokers typically transition from light, intermittent smoking to daily smoking between the ages of 18 and 21 years (White et al., 2009), targeting young smokers may result in higher sustained cessation rates than targeting older smokers (Messer et al., 2008).

We therefore examined the relationship between difficulties in emotion regulation and resting-state functional connectivity of the amygdala in young daily smokers and nonsmokers. Our hypotheses were that (1) smokers would self-report higher scores on the DERS than nonsmokers; (2) smokers would exhibit weaker resting-state functional connectivity of the amygdala with those regions identified as important for emotion regulation: bilateral prefrontal cortex, bilateral insula, left ACC, left middle temporal gyrus, and superior parietal lobe; and (3) connectivity of the amygdala with these regions would be associated with a greater negative correlation with DERS scores in smokers than in nonsmokers. The examination of this final hypothesis is the most pertinent to our aim of providing information to aid smoking cessation efforts, as determining whether smokers and nonsmokers differ in the neural mechanisms of emotion dysregulation can inform development of novel smoking cessation therapies.

Methods

Data for this study were collected between January 2011 and August 2012 at the University of California, Los Angeles. All procedures were approved by the UCLA Institutional Review Board (IRB# 10-000259).

Participants and Procedures

This study employed a between-patient design with 2 groups: smokers and nonsmokers. Thirty-seven participants (18 smokers, 19 nonsmokers, all 16–21 years of age) were recruited through online advertisements (e.g., craigslist.org). At an intake session, participants gave written informed consent after receiving a detailed explanation of the study with the opportunity to ask questions. Exclusion criteria were positive urine test for illicit drugs (cocaine, methamphetamine, benzodiazepines, tetrahydrocannabinol/ cannabinoids, opiates) on an Instant-View immunoassay urine test (ALFA Scientific Designs, Inc., Poway, CA); self-report of marijuana use >8 times/ mo and alcohol use >5 d/wk; any Axis I psychiatric disorder (DSM IV-R) as assessed by the Structured Clinical Interview for the DSM-IV (First et al. 1995), including current drug abuse or dependence (other than nicotine dependence for those in the smokers group); history of neurological injury or disease; pregnancy; and any contraindication for MRI (e.g., metal implants in the body). Eighteen participants were classified as smokers based on their endorsement of daily smoking for at least 6 months and having carbon monoxide concentrations of >5 ppm in expired air (Smokerlyzer, Bedfont Scientific, Kent, UK). During the intake session, all participants completed the DERS scale, and those who self-identified and met criteria for the smokers group completed the Fagerström Test for Nicotine Dependence (Fagerström, 2012) (see Questionnaire Measures, below). Nineteen participants were assigned to the nonsmoker group because they endorsed having smoked fewer than 5 cigarettes in their lifetimes and had carbon monoxide levels of <5 ppm in exhaled air.

Testing was in the afternoon, and participants were instructed to avoid caffeine for 2 hours beforehand. Smokers were instructed to smoke as usual until 30 minutes before arriving at the testing site to minimize the acute effects of nicotine and of abstinence on resting-state functional connectivity. This abstinence period was selected because smokers report only minimally (albeit significantly) greater withdrawal at 30 minutes compared with <1 minute after smoking a cigarette (Hendricks et al., 2006).

At the beginning of the testing session, participants underwent MRI scanning while in the resting state. These procedures were part of a larger testing battery (data reported in Faulkner et al., 2018a and to be reported elsewhere). For smokers, the average duration of abstinence from smoking prior to the resting state fMRI scan was 49.87 minutes (SD = 41.22 minutes).

Questionnaire Measures

The DERS, a 36-item questionnaire (Gratz and Roemer, 2004), was administered. Scores on this questionnaire range from 1 (“almost never”) to 5 (“almost always”). This questionnaire is comprised of 6 subscales: lack of emotional awareness (6 items), lack of emotional clarity (5 items), limited access to emotion regulation strategies (8 items), nonacceptance of emotional responses (6 items), difficulty in engaging in goal-directed behavior (5 items), and impulse-control difficulties (6 items). All items from each subscale are summed to produce a total score, with higher scores reflecting greater difficulties in emotion regulation. The DERS was reported to have good construct validity and strong internal consistency in a study of 870 adolescents with emotion dysregulation (Neumann et al., 2010) as well as studies of 592 adults with severe mental illness (Fowler et al., 2014) and 207 adult chronic pain patients (Kökönyei et al., 2014). The Fagerström Test for Nicotine Dependence (FTND), a 10-item questionnaire (Fagerström, 2012), was administered as well. Scores on this questionnaire range from 0 (no dependence) to 10 (high dependence).

Behavioral Analyses

Behavioral data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL). The effect of group on total DERS scores as well as on scores from each of the 6 subscales was assessed using separate linear mixed models with group (smoker/nonsmoker) added as a factor. Because females may experience greater difficulties in emotion regulation than males during late adolescence (Bender et al., 2012) and emergent adulthood (Zimmerman and Iwanski, 2014) and because sex influences smoking behaviors in early adulthood (e.g., Faulkner et al., 2018b), sex/gender was also added to the model as a separate factor to control for this variable.

The effect of group on scores from each of the DERS subscales was only assessed when a significant effect of smoking status on total DERS scores had been observed; Bonferroni correction for the 6 subscales was also performed. The distributions of all data were normal, nonskewed, and with no excess kurtosis.

fMRI Data Acquisition

Resting-state fMRI images were acquired over 5 minutes using a 3-T Siemens AG Trio MRI system with a 12-channel coil while participants viewed a black screen (152 T2*-weighted echoplanar images; repetition time = 2 seconds; echo time = 30 milliseconds; slice thickness = 4 mm; flip angle = 90°; matrix: 64 × 64; field of view = 192 mm). A T2-weighted matched-bandwidth anatomical scan was acquired for initial registration, and a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan was acquired for further registration, including spatial normalization to standard space (Montreal Neurological Institute [MNI]).

fMRI Data Preprocessing

Image analysis was performed using the FMRIB Software Library (FSL) version 5.0.9 (www.fmrib.ox.ax.uk/fsl). The time-course of the resting state fMRI data was first realigned to compensate for small head movements (Jenkinson et al., 2002). All nonbrain matter was removed using FSL’s brain extraction tool. Time-series statistical analysis was carried out using FMRIB’s Improved Linear Model, with local autocorrelation correction (Woolrich et al., 2001) after high-pass temporal filtering (Gaussian-weighted least square fit [LSF] straight line fitting, with sigma = 50 seconds).

None of the fMRI data sets were deemed to have had excessive head motion (>2.5 mm translation). Motion cleaning and noise reduction were performed using a 32-parameter linear regression model (Satterthwaite et al., 2013) that included 6 motion parameters (3 translational dimensions along X, Y, and Z axes and 3 rotational dimensions: “pitch,” “roll,” and “yaw”) combined with the time-series from the cerebrospinal fluid (CSF) and white matter to provide 8 parameters, the temporal derivatives of these parameters, and the quadratic of all parameters, resulting in 32 parameters in total. In addition, frame-wise displacement (FD) was determined with root-mean-squared matrix calculation (using FSL’s “fsl_motion_outliers” tool) to obtain the average rotation and translation parameter differences across images. Time points where motion exceeded acceptable FD thresholds were “censored” by using separate regressors for each of these time points in the model (Power et al., 2012, 2013). A fixed FD threshold for all participants was determined by calculating the SD of FD across all data and computing the following equation: 0.25 mm + 2 * SD (Satterthwaite et al., 2013). The time series of the resultant residuals from the regression model was then scaled and normalized at each voxel: ([residuals—mean]/SD) + 100.

A seed-based approach was implemented with a mask of the bilateral amygdalae created in the Harvard Oxford Atlas in FSL (see supplementary Figure 1). The center-of-mass (in MNI space) of the right amygdala was $x=32$, $y=61$, $z=27$, and this region extended from $x=29$ to 39, $y=56$ to 65, and $z=23$ to 30. The center of mass of the left amygdala was $x=56$, $y=60$, $z=27$, and this region extended from $x=51$ to 60, $y=56$ to 63, $z=23$ to 31. These masks were transformed to each participant's native space. For each participant, time series data from each voxel in both amygdalae were extracted from the scaled and normalized residuals of the 32-parameter regression model, averaged, and included as a single explanatory variable in a linear model. Contrast images representing voxel-wise effects resulting from the linear model were registered through a 3-step procedure: Echo planar imaging (EPI) images were first registered to the matched-bandwidth structural image, then to the MPRAGE structural image, and finally into standard (MNI) space using 12-parameter affine transformations (Jenkinson and Smith, 2001). Registration from MPRAGE structural images to standard space was further refined using nonlinear registration (FSL's FNIRT) (Andersson et al., 2007). Images were smoothed using a 5-mm full-width at half-maximum Gaussian kernel.

fMRI Data Analysis

Group-level analyses were performed using FSL's FMRIB's Local Analysis of Mixed Effects with outlier deweighting applied. To assess the influence of group (smoker, nonsmoker) on the relationship between difficulties in emotion regulation and resting-state functional connectivity, models were constructed with 4 explanatory variables (EVs). The first EV denoted nonsmokers, the second EV denoted smokers, the third EV denoted (demeaned) DERS scores for nonsmokers, and the fourth EV denoted (demeaned) DERS scores for smokers. Two contrasts were computed to test the difference in the slopes between nonsmokers and smokers that represents the linear relationship between amygdala RSFC and DERS scores. The first contrast indicated the effect of the difference in slopes for nonsmokers vs smokers, and the second contrast indicated the reverse (difference in smokers vs nonsmokers). Statistical maps were cluster-corrected for multiple comparisons (voxel height threshold: $Z>3.09$, cluster significance $P<.05$).

Because there was a significant effect of group on DERS total scores and on the lack of emotional clarity subscale (but not the other subscales; see below), only 2 general linear models (GLMs) were constructed: one containing the DERS total scores and the other containing scores from the lack of emotional clarity subscale. Scores that were not significantly influenced by group were not included in a GLM.

Results

Participant Characteristics

Of the 37 participants who completed testing, 27 were male and 10 were female (mean age = 19.97 years, SD = 2.20 years). The ratio of males to females did not significantly differ between the smoker and nonsmoker groups ($F[1,35]=0.392$, $P=.535$). Smokers reported an average FTND score of 2.56 (SD = 2.38), consistent with low to moderate nicotine dependence. There was no influence of sex/gender on FTND scores (males: mean = 2.79, SD = 2.42; females: mean = 1.75, SD = 2.36; $F(1,16)=0.573$, $P=.460$). A full description of participant characteristics is shown in Table 1. Finally, smokers and nonsmokers did not significantly differ in level of education ($F[1,35]=3.294$, $P=.071$) or amount of lifetime marijuana use ($F[1,35]=2.171$, $P=.150$).

Table 1. Participant Characteristics

	Smokers	Nonsmokers
n	18	19
Sex (M/F)	14/4	13/6
Age (y)[a]	19.11 (4.60)	19.89 (1.20)
Education (y)	10.78 (1.38)	11.23 (1.45)
Ethnicity (no. of participants)		
White Caucasian	13	12
African American	0	1
Asian American	2	2
Hispanic	2	2
Other	1	2
Cigarette smoking[a]		
Age of first use (y)	16.50 (2.17)	—
Cigarettes per day	9.31 (6.78)	—
Nicotine dependence[a]	2.57 (2.38)	—
Substance use[a]		
Marijuana (days used in past 30)	0.73 (0.48)	0.52 (0.54)
Alcohol (drinks per week)	1.12 (2.31)	0.98 (1.73)

[a] Denotes mean (SD).

DERS

Compared with nonsmokers, smokers had higher total scores on the Difficulties in Emotion Regulation Scale (DERS) ($F[1,33]=6.278$, $P=.017$) (Figure 1A). Post-hoc analyses of data from each subscale revealed that compared with nonsmokers, smokers reported a significantly greater lack of emotional clarity ($F[1,33]=11.485$, $P=.002$); this effect survived Bonferroni correction (corrected $P=.012$) (Figure 1B). Although some of the group comparisons of the other subscales showed suggestive differences between smokers and nonsmokers, these differences did not reach statistical significance when corrected for multiple comparisons.

Specifically, there were no significant effects of group on difficulties in controlling impulsive behaviors ($F[1,33]=5.260$, $P=.028$, Bonferroni-corrected $P=.168$), access to emotion regulation strategies ($F[1,33]=4.987$, $P=.032$, Bonferroni-corrected $P=.177$), acceptance of emotional responses ($F[1,33]=3.641$, $P=.065$, Bonferroni-corrected $P=.332$), lack of emotional awareness ($F[1,33]=2.335$, $P=.136$, Bonferroni-corrected $P=.584$), or difficulties in engaging in goal-directed behaviors ($F[1,33]=0.392$, $P=.535$, Bonferroni-corrected $P=.989$).

Resting-State Functional Connectivity

The neural mechanisms of smoking-related deficits in emotion regulation (as determined by total DERS scores) and in emotional clarity were examined. Because there were no significant group effects on the remaining subscales, the neural correlates of scores on these subscales were not investigated.

Whole-brain, voxel-wise GLM analyses revealed that the relationship between scores on the lack of emotional clarity

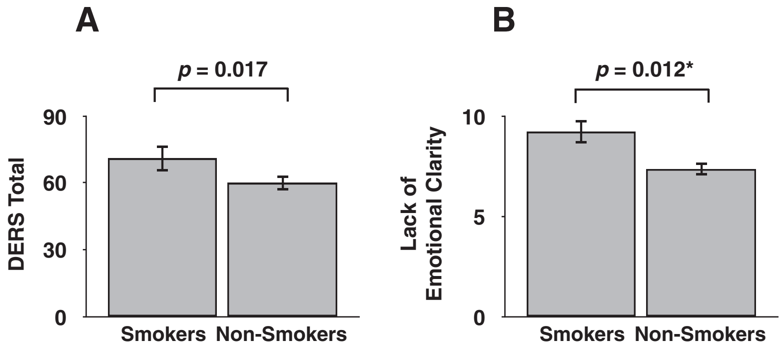

Figure 1. Group differences in Difficulties in Emotion Regulation Scale (DERS) total scores (A) and in scores from the lack of emotional clarity subscale (B). Asterisk in (B) denotes the Bonferroni-corrected P value.

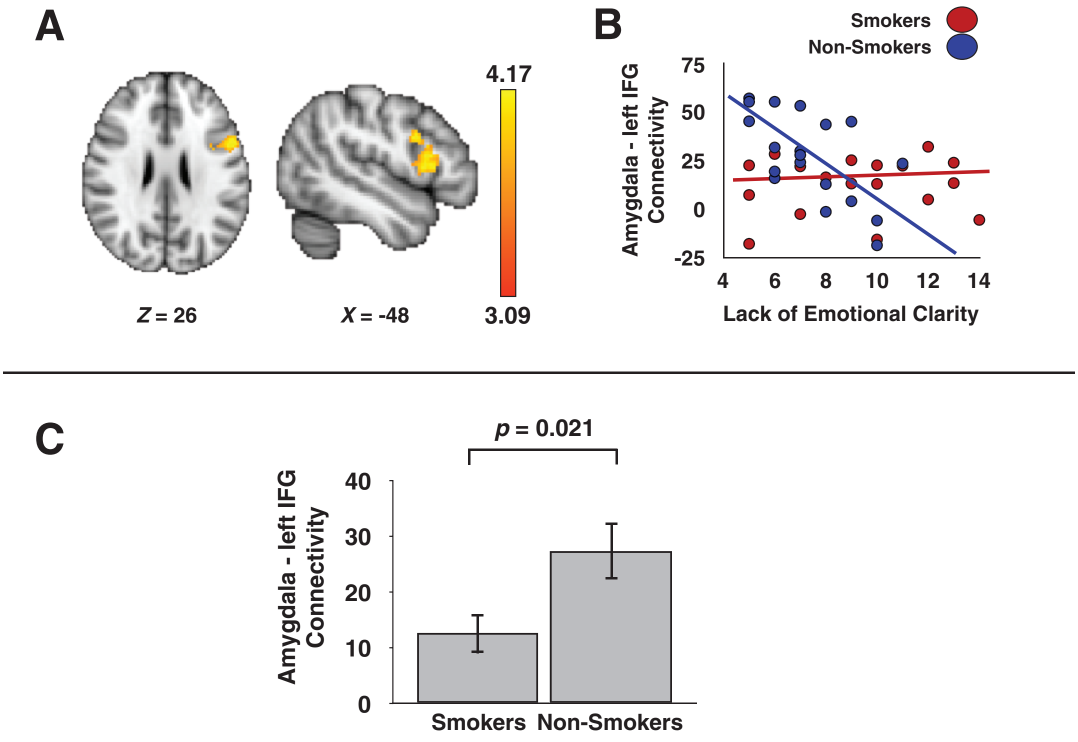

Figure 2. Effect of group on the relationship between resting-state functional connectivity and scores from the lack of emotional clarity subscale of the Difficulties in Emotion Regulation Scale (DERS). (A) Cluster denotes the region in which connectivity with the bilateral amygdala is more associated with a lack of emotional clarity in smokers than in nonsmokers. (B) Correlation of scores from the lack of emotional clarity subscale and z values from the cluster depicted in Figure 2A. (C) Graph depicts mean z values from the clusters shown in Figure 2A, for smokers and nonsmokers separately.

subscale and functional connectivity of the amygdala was influenced by smoking status. Specifically, contrast 1 showed that lack of emotional clarity was negatively correlated with connectivity of the bilateral amygdala with a group of voxels in the left inferior frontal gyrus in nonsmokers more than in smokers (Figure 2A–B). A post-hoc correlation analysis was performed to determine whether the relationship between the amygdala—left inferior frontal gyrus connectivity depicted in Figure 2 and lack of emotional clarity scores existed in both groups separately; this analysis revealed that this relationship existed in nonsmokers ($r = -0.710$, $P = .001$) but not in smokers ($r = 0.113$, $P = .654$).

Connectivity values (z scores) were entered as a dependent variable into a post-hoc ANOVA, which revealed that connectivity of the amygdala with the inferior frontal gyrus was weaker in smokers than in nonsmokers ($F[1,35] = 5.522$, $P = .025$) (see Figure 2C). These connectivity values (z scores) were not significantly related to the duration of abstinence from smoking prior to resting-state MRI scanning ($r = 0.110$, $P = .664$), indicating that this short length of smoking abstinence did not significantly influence resting-state functional connectivity of the amygdala with the inferior frontal gyrus in this sample smokers. There were no significant clusters for the opposite contrast (i.e., contrast 2).

The whole-brain, voxel-wise GLM that examined the effect of group on the relationship between amygdala connectivity and DERS total scores revealed no significant clusters.

Discussion

Compared with nonsmokers, smokers exhibited greater difficulty in emotion regulation, as evidenced by higher DERS total scores and scores on the lack of emotional clarity subscale. In addition, resting-state functional connectivity of the amygdala with the left inferior frontal gyrus was stronger and more negatively correlated with lack of emotional clarity in nonsmokers than in smokers. Thus, an important component of smoking-related difficulties in emotion regulation may be a lack of emotional clarity, and the connectivity between the amygdala and inferior frontal gyrus may be a relevant therapeutic target for increasing this clarity, which may in turn facilitate smoking cessation.

This study of young smokers provides the first direct evidence, to our knowledge, that smokers experience greater difficulties in emotion regulation than nonsmokers, in part due to a lack of emotional clarity. While Farris et al (2016) reported that total DERS scores prior to a quit attempt were positively correlated with the chance of relapse, individual subscales of the DERS were not tested. The current findings indicate that an important component of tobacco-related difficulties in emotion regulation is a lack of emotional clarity. This component is defined by the authors of the DERS as a failure to understand the *characteristics* of an emotion (i.e., valence, intensity, etc.) being experienced. In contrast, the lack of emotional awareness subscale defines a person's failure to appreciate that he or she is experiencing an emotion at all (Gratz and Roemer, 2004). Emotional clarity is considered vital for successful emotion regulation (Gratz and Roemer, 2004), and deficits in emotional clarity are associated with symptoms of depression and anxiety, binge eating, and alcohol use (Vine and Aldao, 2014). Future studies could examine whether improving emotional clarity through use of cognitive behavioral therapies or brain stimulation techniques can increase a smoker's ability to quit successfully.

Our results indicate that smokers have weaker connectivity between the amygdala and left inferior frontal gyrus than nonsmokers. In light of previous research (e.g., Buhle and Silvers et al., 2014; Morawetz et al., 2017a, 2017b), these findings suggest that smokers show weaker top-down control of amygdala reactivity. Relevant to this assertion is a report that examined the neural mechanisms of reappraisal strategies during presentation of 15-second videos that were designed to induce negative emotions (Goldin et al., 2008). The authors reported that reappraisal produced enhanced responses in the left inferior frontal gyrus as well as in the dorsolateral prefrontal, ventrolateral prefrontal, and orbitofrontal cortices during the early period of each video presentation (0–4.5 seconds after onset), and that this was associated with subsequent decreases in amygdala reactivity during the late period of the video presentation (15 seconds after onset). Therefore, improving the ability of the inferior frontal gyrus to exert top-down control over the amygdala, for example through the use of brain stimulation techniques, may increase the capacity of smokers to regulate negative emotions.

While we expected the relationship between emotion dysregulation and resting-state functional connectivity of the amygdala to be stronger in smokers, we actually observed no relationship in this group in contrast to nonsmokers who exhibited a negative relationship. Given that our measure of emotion regulation was based on self-report, the lack of correlation we observed among smokers may reflect diminished insight into self-regulatory processes driven by inferior frontal gyrus (IFG)-amygdala functional connectivity. Impairment of insight among those with addictions (e.g., poor recognition of having a problem, difficulties with interoception) has been noted as a barrier to treatment progress, and associated neural processes, including prefrontal cortex (PFC)-subcortical interactions, have been outlined (Goldstein et al. 2009). Further studies are needed to determine if the lack of relationship between self-report and fronto-amygdala functional connectivity we found would be related to impaired insight.

Although this is the first report that smoking-related lack of emotional clarity is related to weak amygdala-inferior frontal gyrus connectivity, the inferior frontal gyrus has long been implicated in emotional representation. For example, Craig (2009) argued that the anterior insula and adjoining inferior frontal gyrus contain interoceptive representations that provide the basis for understanding the nature (i.e., intensity) of emotion. In addition, Zaki et al (2012) reported that the left inferior frontal gyrus/anterior insula becomes more active when rating the valence of an emotion (i.e., happy vs sad), indicating that these regions function (at least in part) in the interpretation or evaluation of characteristics of emotions. Further, alexithymia, a disorder associated with an inability to understand or characterize the emotion being experienced, is associated with hypoactivity in the inferior frontal gyrus (Kano et al., 2003, 2007; Deng et al., 2013), and reactivity to emotional faces in the inferior frontal gyrus is negatively correlated with alexithymia scores in healthy controls but not in methamphetamine users (Payer et al., 2011).

The role of both the amygdala and the insula in emotion regulation may be dopamine dependent. Evidence for this view comes from observations that total DERS scores positively correlate with dopamine D2-type receptor availability in the amygdala in methamphetamine users as well as in healthy controls (Okita et al., 2016a). Future studies could therefore examine whether the relationship between tobacco-related difficulties in emotion regulation and weaker connectivity of the amygdala with the inferior frontal gyrus is influenced by dopamine function in these 2 regions.

This study has some limitations. The small sample size within each group and limited number of female participants precluded adequate examination of the effect of sex/gender, which may influence emotion dysregulation in adolescents (e.g., Zimmerman and Iwanski, 2014). The small sample size may also have led to Type II errors, specifically when examining the effect of group on DERS subscale scores and when examining associations of connectivity with DERS total scores. In addition, while we have discussed the fact that the lack of a relationship between DERS scores and amygdala–inferior frontal gyrus functional connectivity may be due to the inability of the inferior frontal gyrus to exhibit top-down control over the amygdala in smokers, it is also possible that our failure to detect a relationship between these 2 variables is due to the small sample size of only 18 smokers; however, the slope of the relationship in smokers and nonsmokers was significantly different in our data. Further, while we saw no relationship between amygdala–inferior frontal gyrus functional connectivity and the length of smoking abstinence prior to scanning, Sutherland et al. (2013) reported that 24 hours of abstinence from smoking can influence resting-state functional connectivity of the amygdala with the insula (which is adjacent to the inferior frontal gyrus). While our participants were abstinent for a much shorter amount of time (roughly 50 minutes) than those in Sutherland et al. (2013), it may be that this short abstinence influenced functional connectivity of these 2 regions but that the limited range in the duration of abstinence (44–184 minutes) precluded the detection of a relationship between connectivity and duration of abstinence. In addition, some findings did not reach statistical significance when corrections were made for multiple comparisons, potentially due to the small sample size.

Another potential limitation is that these results, found in young adults, may not be generalizable to the wider age range of smokers because difficulties in emotion regulation can decrease over the lifespan (e.g., Orgeta et al., 2009; Zimmerman and Iwanksi, 2014) and because our young smokers had shorter smoking histories and only mild-to-moderate levels of nicotine dependence compared with emergent adult and older adult smokers (e.g., Li et al., 2015; Bi et al., 2017; Faulkner et al., 2017, 2019). Further, because there has been an increase in the use of electronic nicotine delivery systems such as electronic cigarettes among young smokers, future studies may wish to examine whether young daily smokers of electronic cigarettes also demonstrate difficulties in emotion regulation and whether these difficulties are due to dysfunctional amygdala–inferior frontal gyrus functional connectivity. The use of self-report to determine difficulties in emotion regulation may be another limitation. Finally, a potential limitation is the relatively short duration of our resting-state fMRI scans (5 minutes); however, when resting-state functional connectivity analyses were performed on data collected from 2 to 11 minutes, the average strength of correlation of activity between regions stabilized when approximately 5 minutes of data was used (van Dijk et al., 2010).

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Statement of Interest

Dr London has received speaking fees from Alkermes Pharmaceutical Company. None of the other authors have any conflicts of interest to declare.

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