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GABA Levels in The Dorsal Anterior Cingulate Cortex Associated with Difficulty Ignoring Smoking-Related Cues in Tobacco-Dependent Volunteers

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Substance abusers have difficulty ignoring drug-related cues, which is associated with relapse vulnerability. This 'attentional bias' towards drug cues translates into an inability to ignore drug-related stimuli and may reflect deficits in the brain regions, such as the dorsal anterior cingulate cortex (dACC)—a key region in cognitive control and adaptive decision making. Quantifying relationships between attentional biases to drug cues and dACC neurochemistry could aid in identifying neurobiological mechanisms associated with increased relapse vulnerability precipitated by drug cues. As gamma-aminobutyric acid (GABA) deficits have been linked to impaired cognition and addictive disorders, we hypothesized that reduced GABA in the dACC would be associated with increased attentional biases towards smoking-related cues. We confirmed this hypothesis among nicotine-dependent tobacco smokers by combining an offline behavioral measure of attentional bias with magnetic resonance spectroscopy. Smokers with the greatest attentional bias also experienced more negative affect during early nicotine withdrawal. Findings revealed a relationship between heightened reactivity to drug cues, and both decreasing dACC GABA and early withdrawal symptoms. Because reduced GABA function in frontal brain regions disrupt cognitive function, our findings suggest that smokers with diminished dACC GABA may lack the cognitive resources to successfully ignore highly salient distractors such as tobacco-related stimuli and therefore might be more prone to cue-induced relapse. This newly discovered relationship between dACC GABA and attentional bias provides evidence for a neurochemical target, which may aid smoking cessation in highly cue-reactive individuals.

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INTRODUCTION

Dependence on tobacco-derived nicotine continues to be a global health epidemic (World Health Organization, 2008). Unfortunately, most smokers are unable to maintain long-term abstinence (Gonzales *et al*, 2006; Hughes *et al*, 2003), highlighting the need to develop more effective treatments and novel approaches for identifying relapse prone individuals. One difficulty in developing effective smoking cessation therapies is that individuals may continue to smoke owing to a range of factors, suggesting that more specialized treatment approaches targeting specific risk factors are needed. Reactivity to smoking cues is one factor associated with cigarette craving, which may precipitate relapse. In fact, probing cue reactivity using a modified version of the Stroop task, which assesses the ability to perform a primary task within the context of distracting smoking-related cues, has shown promise for predicting smoking cessation outcomes (Waters *et al*, 2003; Janes *et al*, 2010a).

Successful performance on the smoking emotional Stroop (SES) task requires that participants ignore smoking-related cues in favor of task elements unrelated to smoking. The inability to efficiently ignore drug-related stimuli (ie, an attentional bias towards drug cues) may reflect deficits in frontal brain regions critically implicated in cognitive control and decision making, which may contribute to the persistence of drug addiction (Goldstein and Volkow, 2011). In particular, the dorsal anterior cingulate cortex (dACC) has a key role in addiction as this region is not only implicated in smoking cue attentional bias (Luijten *et al*, 2012), but also reward-based decision making, conflict monitoring (Botvinick, 2007; Bush *et al*, 2002), and cognitive regulation of smoking cue-induced craving (Brody *et al*, 2007). In line with this conjecture, the dACC has been found to be dysfunctional in more heavily nicotine-dependent smokers (Hong *et al*, 2009) as well as those likely to relapse (Janes *et al*, 2010a). Collectively, these

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studies suggest that therapies targeted at ameliorating dACC dysfunction may reduce attentional bias and, as a result, minimize relapse risk. However, neurochemical disruptions within the dACC have yet to be associated with attentional bias for drug cues.

In the present study, we focused on gamma-aminobutyric acid (GABA) concentrations in the dACC, as reduced prefrontal GABA has been associated with impaired cognition (Enomoto *et al*, 2011; Fujiwara *et al*, 2011; Paine *et al*, 2011) and addictive disorders (Behar *et al*, 1999; Ke *et al*, 2004; Levy and Degnan, 2012). Additionally, GABAergic agonists reduce cigarette consumption in clinical trials (Franklin *et al*, 2009), and disrupt reactivity to nicotine cues in preclinical studies (Paterson *et al*, 2005). Specifically, we assessed the relationship between attentional bias towards smoking-related words using the SES task and dACC GABA concentrations using proton magnetic resonance spectroscopy (^{1}H-MRS) in nicotine dependent smokers. To test whether attentional bias was associated with early nicotine withdrawal symptoms, we also evaluated the relationship between attentional bias and changes in mood and craving due to short-term nicotine abstinence. Our findings provide novel insights into the neurobiological substrates of attentional bias, and may offer early evidence that GABA may represent a neurochemical target for treating cue-reactive smokers.

MTERIALS AND METHODS

Study Participants

Fifteen nicotine-dependent tobacco smokers (eight women) between the ages of 18–33, who did not participate in our previous studies (Janes *et al*, 2010a,b), underwent neuroimaging and behavioral testing at the McLean Imaging Center of McLean Hospital. Participants reported smoking $\geqslant$10 cigarettes/day over the past 6 months, and were moderately to heavily nicotine dependent as measured by the Fagerstrom test for nicotine dependence (FTND; Fagerstrom, 1978). Participants were assessed by the Structured Clinical Interview for DSM and met criteria for current nicotine dependence. Participants were excluded if they had a lifetime diagnosis of the following conditions: organic mental disorder, bipolar or unipolar depression, and schizophrenia spectrum disorder. Participants were excluded for current substance use disorder other than nicotine dependence. Smokers also were excluded for pregnancy, current psychotropic drug use, recent drug use, or excessive alcohol use. Subjects were recruited using online advertisements and fliers posted in the Boston area. All participants provided written informed consent before participating in any study procedures, and the institutional review board at McLean Hospital approved this study.

Participant Assessments

Lifetime tobacco use was assessed by pack-years, while recent smoking was measured by expired carbon monoxide (CO; Micro Smokerlyzer II, Bedfont Scientific Instruments). Cigarette craving was assessed by the Tiffany Questionnaire of Smoking Urges (QSU; Tiffany and Drobes, 1991), whereas the Barratt Impulsiveness Scale (BIS; Patton *et al*, 1995) was used to measure impulsivity. State affect also was measured using the Positive and Negative Affect Schedule (PANAS; Watson *et al*, 1988). To standardize the time since a cigarette was last smoked, all participants smoked one of their own cigarettes at the beginning of the study. MRS was measured $\sim$2.5 h after smoking while the Stroop task was administered $\sim$4.5 h after smoking. To assess the onset of withdrawal-induced craving and negative mood, both the QSU and PANAS were administered $\sim$1 h after smoking and again $\sim$3.5 h after smoking. Specifically, we focused on increases in negative affect using the negative subscales of the PANAS (Watson *et al*, 1988). Changes in craving and negative affect were calculated by comparing responses made at 3.5 *vs* 1 h post smoking.

To rule out the possibility that sex differences might be driving any effects, all measures were compared between men and women using two-tailed *t*-tests. Additionally, menstrual cycle phase was obtained in women using self-report, and all measures were compared between women in the luteal *vs* follicular menstrual cycle phase.

Magnetic Resonance Spectroscopy

Data acquisition. MRS data were collected on a 3T Siemens TRIO Tim, whole-body, clinical MR system (Erlangen, Germany) using a 32-channel phased-array design RF head coil operating at 123 MHz for proton imaging and spectroscopy. High-resolution T1-weighted anatomical images were used to position a single $2 \times 2 \times 3$ cm voxel in the dACC (Figure 1). Proton MRS used a modified J-resolved PRESS protocol (two-dimensional (2D)-JPRESS). Shimming of the magnetic field within the prescribed voxel was done automatically using an automated shimming routine. Following the additional automated optimization of water suppression power, carrier frequency, tip angles, and coil tuning, the 2D-JPRESS sequence collected 22 echo time (TE)-stepped spectra with the TE ranging from 30 to 350 ms in 15 ms increments. Acquisition parameters were: repetition time = 2 s, f1 acquisition bandwidth = 67 Hz, spectral bandwidth = 2 kHz, readout duration = 512 ms, NEX = 16/TE-step, total scan duration = 12 min.

Proton MRS processing/analysis. All spectroscopic data processing and analysis was undertaken on a LINUX

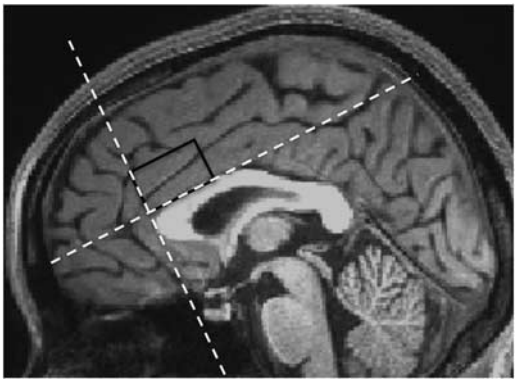

Figure 1 Sagittal view of a representative T_1-weighted image illustrating $2 \times 2 \times 3$ cm voxel placement in the dACC.

workstation. In order to quantify GABA with the JPRESS data, the 22 TE-stepped free-induction decay was first zero-filled out to 64 points, Gaussian-filtered, and Fourier transformed. Consistent with our validated methods, every J-resolved spectral extraction within a bandwidth of 67 Hz was fitted with LCModel and its theoretically-correct template, which used an optimized GAMMA-simulated J-resolved basis sets modeled for 2.89 T (Friedman *et al*, 2012; Henry *et al*, 2011; Jensen *et al*, 2009). The integrated area under the entire 2D surface for each metabolite was calculated by summing the raw peak areas across all 64 J-resolved extractions for each metabolite. GABA metabolites were expressed as ratios to total creatine (Cr). A representative spectrum is shown in Figure 2.

Image Segmentation/voxel Tissue Analysis

All image segmentation was performed using FSL version 4.1.1 (FMRIB Software Library; Analysis Group, FMRIB; Oxford, UK) in a VMware virtual machine running on a PC. For voxel tissue partial-volume estimation, the high-resolution T_1-weighted axial images were first automatically segmented into cortical gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) compartments using the segmentation tool in the software package FSL 4.1.1. This package allows for optimized and fully automated segmenting of both cortical tissue ('FAST'—FMRIB Software Library; Analysis Group, FMRIB; Oxford, UK) as well as sub-cortical tissue ('FIRST'—FMRIB Software Library; Analysis Group, FMRIB; Oxford, UK). The segmented images were then reformatted for input into an automated voxel coregistration and partial-volume analysis in-house program written in C-code. Subsequently, the volumetric tissue contribution for each oblique dACC voxel was determined and volumetric contributions of total GM, WM, and CSF calculated.

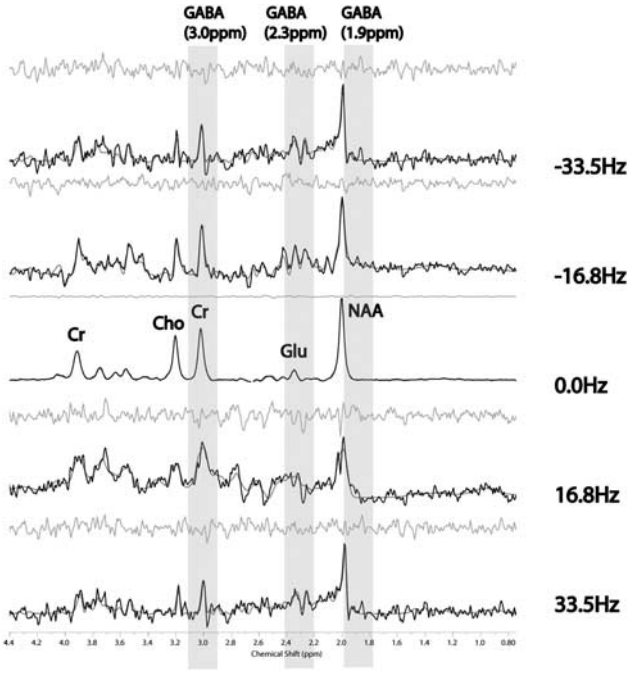

Figure 2 Selected J-resolved spectral extractions across the 67 Hz bandwidth in the J-resolved 2D spectrum, displayed with 1 Hz exponential time-domain filtering and LCModel fits. Displayed spectral extractions are a subset of the 64 J-resolved spectra from, which GABA is derived using LCModel. Each spectral extraction is modeled with its specific theoretical J-resolved LCModel template and the output from each extraction integrated across all 64 extractions to derive the final metabolite areas.

Smoking Emotional Stroop

Participants performed a behavioral computerized SES task outside of the magnet $\sim$4.5 h after smoking and 2 h after MRS scanning. The SES task displayed neutral and smoking associated words, matched for length, and use frequency in the English language, in red, green, or blue font using similar procedures as implemented by others (Gross *et al*, 1993; Munafo *et al*, 2003; Waters *et al*, 2003; Wetherill *et al*, 2012) and as in our previously published work (Janes *et al*, 2010a,b). Participants were instructed to press a button to identify font color as accurately and quickly as possible while ignoring word meaning. Participants first completed a 96-trial practice block of letter strings followed by two experimental blocks containing 33 trials (words) each. The neutral block preceded the smoking block by a 5 s break and in each block, every word ($n = 11$) was repeated three times (once for each color). Each trial began with a 500 ms fixation cross, followed by a word presentation, and then a 500 ms intertrial interval. Words were presented until a response was made, or disappeared after 3 s if no response was made. Eprime software (Psychology Software Tools, Pittsburgh, PA) was used to present stimuli and record responses. A two step procedure was implemented to minimize outlier response: trials with reaction times (RT) $<$ 150 ms and $>$ 1500 ms were first excluded; next, trials with natural log-transformed RT falling out of the range of mean $\pm$ three SD (calculated for each participant individually after the removal of trials with 150 ms $>$ RT $>$ 1500 ms) were also excluded (on average, 4.5% of the trials were excluded). Following established procedures (eg, Janes *et al*, 2010a,b; Waters *et al*, 2003), an attentional bias score was computed as $RT_{smoking}$–$RT_{neutral}$ for trials with correct responses. Higher values indicate enhanced interference effects associated with smoking-related words.

Correlation Analyses

A Pearson's correlation coefficient was calculated between smoking attentional bias ($RT_{smoking}$–$RT_{neutral}$) and dACC GABA/Cr concentration. To determine whether attentional bias and dACC GABA/Cr levels were associated with changes in mood and craving over short-term nicotine abstinence, correlation coefficients were also calculated between attentional bias, dACC GABA/Cr and changes in QSU and negative affect PANAS scores 3.5 *vs* 1 h after cigarette smoking. Finally, to identify possible relationships between demographic factors and our variables of interest, Pearson's correlation coefficients were also calculated between attentional bias, dACC GABA/Cr, and: age, FTND, expired CO, pack-year, and BIS. To ensure that findings were not unduly affected by possible outliers, correlations were confirmed using Spearman's nonparametric test.

RESULTS

Participant Demographics

On average, participants were 25.5 ± 4.8 (SD) years old, with 15.5 ± 2.2 years of education. Participants had an average FTND score of 6.2 ± 1.1, indicating moderate to heavy nicotine dependence. Participants also reported smoking 15.5 ± 3.8 cigarettes/day, and had an average pack-year of 6.7 ± 4.9 years. Just before MRS procedures, participants had an expired CO of 27.7 ± 12.9 ppm. The average change in negative affect as measured by the PANAS was 0.33 ± 1.63. Over the course of the experiment, cigarette craving significantly increased ($P<0.01$, $t_{14}=3.1$) as measured by the QSU.

SES Main Effect

During the SES task, smokers took an average of 35.38 ± 76.91 ms longer to respond to smoking *vs.* neutral words. Although this difference between smoking and neutral word RT was not statistically significant (likely due to large individual differences), 11 of the 15 participants showed a Stroop interference effect greater than zero (ie, some degree of smoking-related interference). A binomial distribution test indicated that this effect was significant (binomial $p_{(11/15)}=0.042$).

Behavioral and Neurochemical Associations

As hypothesized, a significant negative correlation emerged between attentional bias towards smoking cues and dACC GABA/Cr levels ($r=-0.63$, $P=0.011$; 95% confidence interval (CI): −0.86 to −0.18; Spearman's rho = −0.68, $P<0.01$; Figure 3). Analyses were repeated controlling for age and expired CO, as we found relationships between dACC GABA/Cr and age ($r=-0.54$, $P=0.04$; 95% CI: −0.82 to −0.037) and GABA/Cr, and expired CO ($r=-0.51$, $P=0.05$; 95% CI: −0.81 to −0.002). When controlling for age and CO using a partial correlation, the association between dACC GABA and smoking word attentional bias remained (two-tailed Pearson's $r=-0.61$, $P=0.026$).

A significant positive correlation emerged between enhanced attentional bias to smoking cues and increased negative affect over the course of the experiment, as measured by the PANAS ($r=0.77$, $P<0.001$; 95% CI: 0.42–0.92; Spearman's rho = 0.82, $P<0.001$; Figure 4). Thus, attentional biases toward smoking-related cues increased with increasing levels of negative affect over the course of the experiment. In addition, a trend for a negative correlation emerged between GABA and increased negative affect ($r=-0.46$, $P=0.08$; 95% CI: −0.79 to 0.07). There was no relationship between FTND, BIS, pack-year, or QSU-measured craving and attentional bias or dACC GABA/Cr levels. All associations with dACC GABA/Cr levels were unrelated to Cr, which was the internal reference for each participant.

Sex Differences

No differences were found between men and women on any measure. Of the eight women studied, four were in the luteal phase and four were in the follicular phase of their menstrual cycle. No differences were found between women in different phases of their menstrual cycle.

Voxel Tissue

On average, the dACC voxel was comprised of 58.8 ± 5.7 percent GM, 30.8 ± 4.5 percent WM, and 10.44 ± 3.9 percent CSF. We found no significant correlation between GABA levels and the amount of GM, WM, and CSF in the defined voxel.

DISCUSSION

In addition to finding a significant percentage of participants with an attentional bias toward smoking cues, we report a negative correlation between attentional bias and dACC GABA/Cr concentration. Our finding that decreasing

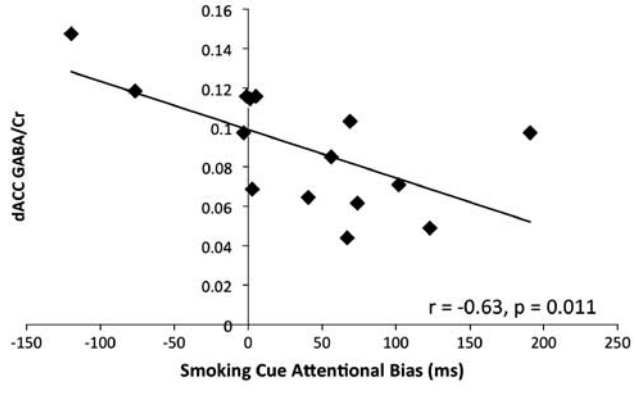

Figure 3 Correlation between smoking cue attentional bias and dACC GABA/Cr. The x axis represents smoking cue attentional bias, which was calculated by $RT_{smoking}$–$RT_{neutral}$ (ms), and the y axis shows the dACC concentration of GABA/Cr. Smokers with the greatest smoking cue attentional bias also had the lowest levels of dACC GABA/Cr ($r=-0.63$, $P=0.011$).

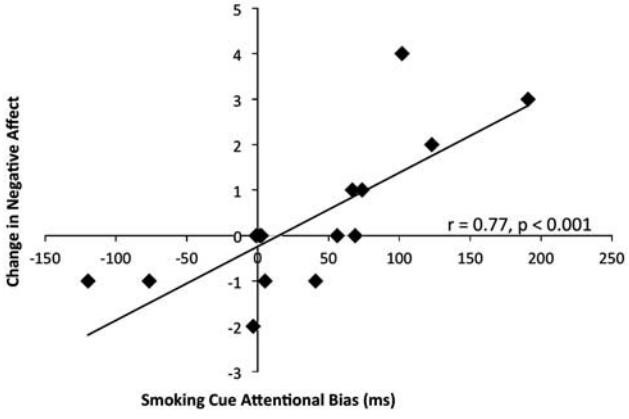

Figure 4 The x axis represents smoking cue attentional bias, which was calculated by $RT_{smoking}$–$RT_{neutral}$ (ms), and the y axis shows the change in negative affect as measured by the PANAS 3.5 *vs* 1 h post smoking. Smokers with the greatest smoking cue attentional bias also experienced the greatest increase in negative affect over the course of the experiment ($r=0.77$, $P<0.001$).

dACC GABA levels were associated with poorer SES performance supports the concept that the dACC has a critical role in attentional biases toward smoking-related cues (Luijten *et al*, 2011) and cognitive control in general (Botvinick, 2007; Bush *et al*, 2002). During tasks requiring cognitive effort, such as those containing distracting stimuli, the dACC along with other prefrontal brain regions is critically implicated in focusing attention away from the distractors and sustaining task-related goals (Botvinick, 2007; Bush *et al*, 2000; Bush and Shin, 2006; Medalla and Barbas, 2009). During the SES task, intact and efficient dACC function may be necessary for smokers to ignore the irrelevant smoking stimuli and attend to information necessary to perform the primary task. Disruptions in this system may therefore lead to interference by smoking stimuli.

Reductions in dACC GABA/Cr may contribute to smoking cue attentional bias as mounting evidence indicates that low levels of prefrontal GABA contribute to attentional and cognitive dysfunction at a more basic level (Enomoto *et al*, 2011; Fujiwara *et al*, 2011; Paine *et al*, 2011; Pehrson *et al*, 2013). On a cellular level, GABA enhances neuronal communication by inhibiting inappropriate activation or 'noise' while allowing selective activation of task-relevant signals, thus facilitating optimal cognition (Paine *et al*, 2011; Rolls *et al*, 2008; Winterer and Weinberger, 2004). Although reduced prefrontal GABA is thought to partly explain cognitive deficits in schizophrenia (Enomoto *et al*, 2011; Paine *et al*, 2011; Rolls *et al*, 2008) and age-related cognitive decline (Fujiwara *et al*, 2011), the current findings suggest that lower levels of prefrontal GABA may account for cognitive interference by smoking cues in otherwise healthy, young smokers. Specifically, lower dACC GABA may reduce the ability to filter irrelevant information leading to distraction by salient stimuli such as smoking cues.

Similar to attentional bias, negative mood has been associated with smoking relapse vulnerability (Shiffman and Waters, 2004), suggesting that these factors may be important targets for smoking cessation treatments. Consistent with previous findings (Bradley *et al*, 2007), we uncovered a strong positive relationship between negative mood and smoking attentional bias, implying that these two relapse vulnerability risk factors may be linked. In fact, negative affect generally disrupts cognitive performance during interference tasks (Sommer *et al*, 2008), indicating that a more global association exists between affect and cognitive interference. Not only do negative emotions lead to greater interference measured behaviorally, but also negative affect reduces dACC activation during interference processing (Sommer *et al*, 2008). One hypothesis is that the dACC may be the neurobiological link between negative affect and cognition (Shackman *et al*, 2011; Sommer *et al*, 2008). Therefore, smokers experiencing negative affect may have greater difficulty ignoring smoking cues owing to the influence of negative mood on dACC function. When smokers with relatively lower levels of dACC GABA experience negative affect, this may tax an already dysfunctional dACC, making it even more difficult to ignore salient distractors such as smoking cues. We also found a trend negative association between dACC GABA/Cr and negative mood. Given the relationship between reduced brain GABA concentrations and mood disorders (Brambilla *et al*, 2003; Petty, 1995), it is possible that a lower dACC GABA concentration may enhance the likelihood of experiencing nicotine withdrawal-induced negative affect. Although plausible, this proposed relationship between dACC GABA and nicotine withdrawal requires confirmation in a larger sample of smokers.

Although the relationship between decreased cortical GABA and substance abuse has been previously established (Ke *et al*, 2004; Behar *et al*, 1999, Levy and Degnan, 2012), this is the first reported association between dACC GABA/Cr concentration and smoking attentional bias. GABA-based therapies have been explored for numerous addictive disorders (eg, Brebner *et al*, 2002; Brodie *et al*, 2003; Franklin *et al*, 2009; Kampman *et al*, 2004; Kaplan *et al*, 2003) and have been found to reduce cigarette consumption (Franklin *et al*, 2009) and cigarette craving (Sofuoglu *et al*, 2005). Preclinically, GABAergic drugs improve drug-induced cognitive disruptions (Arai *et al*, 2009; Porrino *et al*, 2012) and reduce responding to nicotine cues (Paterson *et al*, 2005). Additionally, GABAergic drugs enhance traditional Stroop performance in clinical studies (Sofuoglu *et al*, 2005). These studies suggest that pharmacological enhancement of GABAergic function may not only reduce smoking, but may buffer against future relapses by improving cognitive deficits such as those contributing to smoking attentional bias.

Cigarette craving increased over the course of the experiment, yet we did not find an association between craving and attentional bias, which is consistent with a meta-analysis showing that the relationship between tobacco craving and attentional bias is weak, especially when using behavioral measures such as the SES (Field *et al*, 2009). Also consistent with previous research, we found no influence of sex on attentional bias and nonabstinent negative affect (Leventhal *et al*, 2007). Nevertheless, while some brain regions experience GABA fluctuations due to menstrual cycle phase, ACC GABA levels are unaffected by the menstrual cycle (Harada *et al*, 2011). Additionally, smoking is thought to abolish the influence of the menstrual cycle on occipital cortex GABA fluctuations such that women smokers do not experience a rise in GABA during the follicular phase (Epperson *et al*, 2005). On the basis of these past studies, menstrual cycle influences on our results were unlikely. However, given our small sample size and the variability of self-reported menstrual cycle phase information, the influence of sex on the relationship between dACC GABA/Cr and attentional bias needs to be tested more directly.

LIMITATIONS

Despite the wealth of research suggesting prefrontal GABA has a role in cognition (Enomoto *et al*, 2011; Fujiwara *et al*, 2011; Paine *et al*, 2011; Pehrson *et al*, 2013; Rolls *et al*, 2008; Winterer and Weinberger, 2004), our results are correlative and thus we are unable to determine whether decreased dACC GABA/Cr directly causes enhanced attentional bias. Furthermore, we have not directly confirmed that GABA levels are stable during the time between the MRS scan and the Stroop task. However, past work suggests that cortical

GABA levels do not change following 48 h of nicotine abstinence (Epperson *et al*, 2005), suggesting that it is unlikely that GABA levels would have changed dramatically over the 2 h between the MRS scan and Stroop task performance. The stability of GABA following 48 h of abstinence also suggests that the individual variability in GABA reported here was not due to early nicotine withdrawal, but may be a pre-existing condition. While this interpretation is plausible based on the prior literature, it needs to be tested empirically.

In the present study, the participant population was restricted to relatively young, healthy smokers with moderate to high levels of nicotine dependence. Our participants were also well educated (having received an average of 15.5 ± 2.2 years of schooling) and showed no influence of trait impulsivity on attentional bias, negative affect, and GABA levels. Therefore, we are unable to generalize the association between GABA and attentional bias to more global cognitive disruptions in this population. Additionally, we found no correlations between GABA levels and specific tissue concentrations in the dACC voxel, suggesting the relationship between GABA and attentional bias to smoking cues is due to individual differences in GABA levels rather than tissue differences within the dACC voxel. However, the relatively limited sample size also suggests that the current finding should be interpreted cautiously. However, future research involving a larger, more diverse sample of smokers may help clarify some of these issues.

As our population consisted entirely of smokers, we cannot conclude that smokers with enhanced attentional bias have a decrease in GABA relative to normative values. However, given the wealth of literature associating lower GABA levels with disrupted cognition and addictive disorders, it is possible that highly cue-reactive smokers have reduced GABA levels. Finally, MRS also limits our results as this method cannot pinpoint the cause of reduced GABA concentrations, nor can it distinguish between separate pools of GABA (eg, intra- *vs* extracellular). Future preclinical work may be useful in clarifying the direct cause of dACC GABA associations with attentional bias.

CONCLUSION

Despite these limitations, the relationship between decreasing dACC GABA/Cr and increasing attentional bias suggests that GABAergic treatments may be helpful for the subset of smokers who are more distracted by smoking cues. Within our sample, there was a range of Stroop RT scores, emphasizing that smokers are not homogeneous in their reactivity to smoking stimuli. This variability is consistent with past work showing that relapse vulnerable smokers have significantly greater attentional bias to smoking cues than smokers able to maintain abstinence (Janes *et al*, 2010a; Waters *et al*, 2003). This sample of studied smokers also included those who more easily ignored smoking *vs* neutral words. Quicker response times to smoking *vs* neutral words has been shown in nonabstinent smokers, as they may not be as preoccupied by smoking cues as abstinent smokers (Gross *et al*, 1993). Our work extends this finding by suggesting that smokers vary in their level of attentional bias, which is associated with dACC GABA levels. Accordingly, therapies that address a possible GABAergic deficit may reduce smoking cue attentional bias and enhance cessation success in cue-reactive smokers. Future research should determine whether our finding is unique to nicotine dependence or whether reduced GABA levels contribute to enhanced attentional bias to drug stimuli across addictive disorders. As attentional bias for drug cues is predictive of treatment outcomes across many addictive disorders including nicotine, alcohol, and heroin (Fadardi and Cox, 2008; Janes *et al*, 2010a; Marissen *et al*, 2006; Waters *et al*, 2003), therapeutics targeting the GABA system may be successful relapse prevention aids for individuals abusing a variety of substances.

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DISCLOSURE

ACJ, JEJ, SLF, BdeBF, and SEL declare no conflict of interest. DAP has received consulting fees from AstraZeneca, Ono Pharma USA, Shire, and Johnson and Johnson for projects unrelated to the current research.

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