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Intra-individual changes in Stroop-related activations linked to cigarette abstinence in adolescent tobacco smokers: Preliminary findings

Sarah W. Yip^{1,2,*}, Iris M. Balodis^{2,3}, Kathleen M. Carroll², Suchitra Krishnan-Sarin^{2,*}, and Marc N. Potenza^{1,2,4,5,*}

¹The National Center on Addiction and Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

²Division of Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

³Department of Psychiatry and Behavioural Neurosciences, Peter Borris Centre for Addictions Research, McMaster University, Hamilton, ON, Canada

⁴Department of Neurobiology, Yale University School of Medicine, New Haven, CT, USA

⁵Yale Child Study Center, Yale University School of Medicine, New Haven, CT, US

Abstract

Background—Adolescence is a crucial time for initiation of tobacco-smoking. Developing more effective treatment interventions for tobacco-smoking in youth is therefore critical to reduce smoking rates in both adolescent and adult populations. Elucidation of the neural mechanisms of successful behavioral change (abstinence) will allow for improvement of therapies based on known brain mechanisms.

Methods—Twenty-one adolescent tobacco-smokers (14–19 years) participated in functional magnetic resonance imaging (fMRI) during performance of a cognitive control (Stroop) task prior to randomization to smoking cessation treatment (trial of combined nicotine replacement therapy/placebo and contingency management for attendance/abstinence; NCT01145001). Fourteen adolescents also participated in fMRI scanning following completion of the six-week trial. fMRI data were analyzed using random-effects models in SPM12. Paired t-tests were used to identify group-level changes (main effect of treatment exposure) in neural functional responses. Regression

*Corresponding author: Sarah W. Yip, 1 Church Street, 7th Floor, Suite 731, New Haven, CT 06510-3330, USA. Tel.: +1 203 737 4358; fax: +1 203 737 3591; sarah.yip@yale.edu.

*Denotes that senior authorship is shared by Drs. Potenza and Krishnan-Sarin

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models were used to identify individual-level changes associated with treatment-outcomes (percent days abstinent, maximum days of consecutive abstinence).

Results—Main effects of Stroop task performance (contrast of incongruent versus congruent trials) were seen across *a priori* ROIs at both pre- and post-treatment ($pFWE < .05$). At the group-level, no changes in neural responses were found following treatment. However, intra-individual reductions in Stroop-related activity (within the insula and anterior cingulate) were positively associated with measures of smoking abstinence during treatment ($pFWE < .05$).

Conclusions—Abstinence from tobacco during smoking cessation treatment among adolescents is associated with cognitive-control related reductions in neural activity within specific regions (anterior cingulate, insula), suggesting that increases in cognitive efficiency may underlie optimal treatment responses in this population.

Keywords

cigarette; smoking; young adult; nicotine patch; development; quit attempt

1. INTRODUCTION

Adolescence is a critical period for the initiation of tobacco-use and over 85% of adult smokers report initiation during this time (USDHHS, 2014). While there has been significant progress in treatment development for both adolescents and adults (Cahill et al., 2013; Morean et al., 2015; Pbert et al., 2015), the development of more effective treatment interventions for adolescent tobacco-smoking remains critical to reduce tobacco use across adolescent and adult populations. Identification of the neural mechanisms of abstinence from tobacco (e.g., via comparison or pre- versus post-treatment neuroimaging data) can be used to improve existing treatment strategies, reducing the burden of care for therapist and patient (Feldstein Ewing and Chung, 2013; Garavan et al., 2013; Yip et al., 2015). However, the neural mechanisms underlying optimal responses to smoking-cessation (or other substance-use) treatments have not been assessed previously in an adolescent population. Emerging data indicate differential neural structural correlates of tobacco-use in adolescent versus mature adult populations (Gogliettino et al., 2016), thus, assessment of the neurobiology of smoking cessation specifically in an adolescent population appears warranted.

Maturation of cognitive-control processes and related neural circuitry are ongoing throughout adolescence and is not complete until early adulthood (Giedd, 2004; Tottenham et al., 2011; Hardee et al., 2014; Raznahan et al., 2014; Pfefferbaum et al., 2015), and this is hypothesized to contribute to tobacco- and other substance-use initiation during this time (Chambers et al., 2003; Casey et al., 2008; Bava and Tapert, 2010; Herting et al., 2010; Galvan et al., 2011; Casey, 2014; Lydon et al., 2014; Heitzeg et al., 2015). Adolescent substance-users demonstrate increased engagement of cortical and subcortical brain regions during cognitive-control (Stroop) task performance when compared to their non-substance-using counterparts, but do not differ in behavioral task performance, suggesting decreased cognitive efficiency (Banich et al., 2007). Similar findings have been reported in adolescents family-history-positive for alcohol-use disorders (Silveri et al., 2011), raising the possibility

that decreased efficiency of cognitive-control-related neural circuitry may be a vulnerability factor for alcohol and substance misuse.

In adults, changes in neural functional responses during cognitive-control processes following treatment for substance addictions have been reported. Specifically, reductions in functional activity during Stroop task performance within the anterior cingulate (Acc), inferior frontal gyrus (IFG) and midbrain have been reported following behavioral treatment (DeVito et al., 2012). These data suggest that the efficacy of some behavioral therapies in adult substance-users may relate to increases in the efficiency of ‘top-down’ inhibitory control processes (DeVito et al., 2012; Kozasa et al., 2012). Hyper-activation of the Acc during cognitive-control processes has been demonstrated among non-treatment-seeking adult smokers during acute abstinence (Azizian et al., 2010; Froeliger et al., 2012), suggesting that cognitive-control processes may be negatively impacted by nicotine withdrawal. Treatment with the nicotinic agonist bupropion has been shown to reduce neural responses during exposure to smoking cues in adult smokers within regions including the Acc and ventral striatum (VS; Culbertson et al., 2011). It is therefore possible that effective smoking-cessation interventions may also decrease neural responses in these regions in adolescents. However, this possibility remains to be tested empirically.

Prospective data further indicate involvement of regions including the dorsal Acc, insula, dorsal striatum and dorsolateral PFC that relates to tobacco abstinence in adults (Janes et al., 2010; Versace et al., 2014; Sweitzer et al., 2016). We recently demonstrated a significant positive association between pre-treatment neural responses within the Acc, insula and midbrain during cognitive-control (Stroop) task performance and smoking-cessation treatment outcomes (reduction in urinary cotinine) in a sample of adolescents (n=11; Krishnan-Sarin et al., 2013). These data suggest that, as in adult populations (e.g., Janes et al., 2010; Versace et al., 2014), individual variability in pre-treatment neural responses may be prospectively related to smoking abstinence among adolescents. However, how and whether neural functional responses during cognitive control also change as a function of smoking-cessation treatment (i.e., change from pre- to post-treatment) in an adolescent population and whether these changes co-occur with smoking abstinence have yet to be examined. Elucidation of the functional neural mechanisms of abstinence from tobacco in an adolescent population may be used to design more effective treatment interventions specifically tailored to this vulnerable population.

In order to further understanding of the neural mechanisms of smoking abstinence related to treatment in adolescents, this study compares pre- versus post-treatment fMRI data during Stroop task performance. Based on prior work (Xu et al., 2007; Azizian et al., 2010; Janes et al., 2010; DeVito et al., 2012; Froeliger et al., 2012; Krishnan-Sarin et al., 2013; Versace et al., 2014; Sweitzer et al., 2016), we hypothesized functional efficiency of ‘top-down’ inhibitory control regions would change from the beginning to end of treatment, and would be related to abstinence. Specifically, we hypothesized that adolescents would exhibit decreased neural activity during cognitive-control processes within the IFG, Acc and insula following treatment and that this would relate to abstinence. We further hypothesized that these changes would be related to measures of smoking abstinence, such that more

abstinence during treatment would be associated with greater change in neural responses from pre- to post-treatment.

2. METHODS

2.1. Participants and recruitment

Adolescents were recruited as part of a six-week, randomized, placebo-controlled controlled trial (RCT: NCT01145001) of smoking cessation conducted in local high schools that combined nicotine replacement therapy (NRT) and contingency management (CM; behavioral reinforcement for abstinence or for attendance). Participants were randomized to receive either (i) NRT + CM for abstinence; (ii) placebo NRT + CM for abstinence; (iii) NRT + CM for attendance; (iv) placebo NRT + CM for attendance. Participants in the placebo NRT condition received an inactive patch (i.e., no nicotine delivery). All participants received CM for attending appointments (\$5 per appointment), and those in the CM for abstinence condition also received bonus payments of \$5 for abstinence at each appointment with a possible bonus payment of \$25 each week (during the first five weeks) if the participant was abstinent at all assessments that week (three assessments in week one, two assessments in weeks 2–5). During the sixth week of the study participants received a single payment of \$25 for abstinence (single assessment). All participants were given the opportunity to participate in fMRI scanning.

Twenty-one adolescents (8 female, 13 male) participated in baseline fMRI scanning prior to randomization to treatment. One adolescent male discontinued the study subsequent to scanning but prior to randomization. For the remaining participants (n=20), randomization groups were as follows: NRT+CM for abstinence (n=5); NRT+CM for attendance (n=7); placebo+CM for abstinence (n=3); placebo+CM for attendance (n=5).

Fifteen (75%) of the 20 randomized adolescents who participated in baseline scanning completed the six-week treatment, consistent with the overall completion rate of the parent RCT (data not yet published; NCT01145001). Of these individuals, all but one participated in post-treatment fMRI scanning, resulting in a total of 14 adolescents with complete pre- and post-treatment fMRI data. Further details on subject participation are shown in Supplemental Figure 1¹.

2.2. Baseline measures

Baseline nicotine-withdrawal symptoms were assessed using the Minnesota Nicotine Symptom Withdrawal Scale (MNWS; Hughes, 1992), a well-validated self-report measure (Hughes et al., 1991) recommended for use in clinical trials (Shiffman et al., 2004; Toll et al., 2007). Pretreatment nicotine levels were assessed via analysis of urinary cotinine, as in prior work (Krishnan-Sarin et al., 2013). Other demographic and smoking-related variables (cigarettes per day, age started smoking daily, years of smoking, modified Fagerstrom Test for Nicotine Dependence (Prokhorov et al., 1996) scores) are shown in Table 1.

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

2.3. Abstinence during treatment

Our earlier fMRI work in adolescent smokers (Krishnan-Sarin et al., 2013) quantified abstinence during treatment using urinary cotinine. Given the use of NRT (which would also increase cotinine levels) in the present investigation, abstinence was quantified using self-report, as determined using the timeline follow-back method at weekly visits to the clinic. As both sustained periods of continuous abstinence (e.g., maximum duration of consecutive abstinence) - and total non-consecutive days of abstinence (e.g., percent days abstinent) – are considered clinically meaningful (Hughes et al., 2003; Kadden et al., 2007; Carroll et al., 2014; Yip et al., 2014), both of these variables were selected for inclusion in the present study.

2.4. Stroop task

Neural responses during cognitive control were assessed using a version of the classic Stroop color-word interference task (Stroop, 1935), adapted for fMRI scanning as in previous studies (Potenza et al., 2003; Brewer et al., 2008; DeVito et al., 2012; Krishnan-Sarin et al., 2013). During performance of the fMRI Stroop task participants are frequently presented with matched color-word pairs (e.g., 'BLUE' printed in blue ink; congruent trials; ~93.5%) and are infrequently presented with mismatched color-word pairs (e.g., 'BLUE' printed in red ink; incongruent trials; ~6.5% of trials). Behavioral and fMRI analyses focus on the contrast between BOLD signals during presentation of incongruent versus congruent trials ('Stroop effect').

2.5. Data acquisition

Functional data were acquired during Stroop performance using a Siemens Trio 3T scanner and a T2*-sensitive echo-planar image (EPI) gradient-echo pulse sequence with the following parameters: repetition time/echo time [TR/TE]=1500/27ms, flip angle=60°, field of view (FOV)=220×220mm, matrix=64×64, 3.4×3.4mm in-plane resolution, slice thickness=4mm with 1mm skip, 5mm effective slice thickness, 25 slices. During scanning, word stimuli were presented for 1300msecs with an inter-trial interval of 350msecs over six runs with 105 stimuli per block.

2.6. fMRI analyses

2.6.1. Regions-of-interest (ROIs)—Based on previous findings in an independent sample (Krishnan-Sarin et al., 2013), the inferior frontal gyrus (IFG), anterior cingulate cortex (Acc), insula and VS were selected as *a priori* ROIs. The IFG, Acc and insula ROIs were defined anatomically (and thus included all subregions) using the corresponding Talairach Daemon (TD) labels in wfu_pickatlas in SPM8; i.e., the IFG was defined using the TD label 'Inferior Frontal Gyrus', the Acc was defined using the TD label 'Anterior Cingulate', and the insula was defined using the label 'Insula'. As in previous studies, e.g., (Breiter, 2001; Balodis et al., 2013), the VS was defined using 10mm spheres centered on [x ±12, y=7, z=-10]. ROIs are shown in Supplemental Figure 2. Family-wise-error (FWE) corrections for multiple comparisons for each of the *a priori* ROIs was conducted using small-volume-correction (SVC) (pFWE<.05).

2.6.2. Pre-processing and subject-level statistics—Spatial pre-processing, subject-level and group-level statistics were conducted using SPM12 (Wellcome Functional Imaging Laboratory, London, United Kingdom). Functional scans were realigned separately prior to normalization to Montreal Neurological Institute (MNI) standard space (voxel size=3×3×3mm³). Scans with participant motion in excess of 4mm or 4° were excluded. Data were smoothed with a 6mm full-width-half-maximum (FWHM) Gaussian kernel. Onsets of task events were convolved with the hemodynamic response function and modeled with temporal derivatives. Models were high-pass filtered at 128sec and included motion parameters from realignment as regressors-of-no-interest.

2.6.3. Group-level statistics

2.6.3.1. Stroop effect: Main effects of Stroop task performance (contrast of incongruent versus congruent trials at pre-treatment and at post-treatment) on neural responses were assessed using linear t-contracts.

2.6.3.2. Pre- versus post-treatment: Within-group differences in Stroop-related neural responses at pre- versus post-treatment were assessed using a paired t-test (contrast of incongruent versus congruent at each time point).

2.6.3.3. Relationship to baseline smoking variables: Associations between Stroop effect (incongruent versus congruent) neural responses and clinical variables at baseline (MNWS scores and cotinine levels) were assessed using multiple regression models.

2.6.3.4. Individual changes in Stroop-related activity and abstinence: To determine the relationship between individual changes in BOLD response and abstinence during treatment, participant difference maps (post- “minus” pre-treatment) were created using imcalc in SPM12. Resultant individual-difference maps were entered into regression models to determine relationships with abstinence.

3. RESULTS

3.1. Demographic and clinical characteristics

Demographic, tobacco, and treatment-outcome variables for the adolescents included in this study are summarized in Table 1. When compared to adolescents who did not participate in fMRI scanning prior to randomization (n=138), the 21 fMRI participants were slightly older (mean±SD=17.00±1.30 versus 16.44±1.21; $F_{(df=158)}=4.32$, $p=0.04$) and had higher baseline MNWS scores (mean±SD=12.30±6.06 versus 8.47±6.24; $F_{(df=153)}=6.60$, $p=0.01$), but did not differ in modified FTND score, cigarettes per day, age on initiation of regular smoking, sex, grade-in-school or baseline cotinine levels ($p>.05$). No differences in abstinence measures (percent days of abstinence during treatment, maximum days of consecutive abstinence) were found between the subset of individuals who participated in fMRI scanning and those of the overall RCT ($p>.05$). Adolescents in both treatment groups reported fewer cigarettes per day at the end of treatment when compared to baseline ($t_{(df=15)}=-8.80$; $p<.001$). As shown in Table 1, no differences in abstinence measures were found between treatment groups (fMRI participants only).

3.2. Behavioral Stroop effects

At both pre- and post-treatment participants had significantly slower reaction times (RTs) on incongruent versus congruent color-word trials (pre-treatment(mean±SD): 719.29±185.63 versus 536.45±44.67; $t_{(df=18)}=-10.33$, $p<.001$; post-treatment: 719.59±101.96 versus 545.38±61.65; $t_{(df=13)}=-8.73$, $p<.001$), consistent with the classic ‘Stroop effect’. No changes in Stroop-related RTs or other performance measures (e.g., errors on incongruent or congruent trials) were seen at pre- versus post-treatment ($p's>.05$).

3.3. fMRI Stroop effects

At both pre- and post-treatment, robust main effects of Stroop task performance (contrast of incongruent versus congruent trials) were seen across all *a priori* ROIs, as well as within regions including the thalamus and caudate (whole-brain findings; shown in Figure 1). At the group-level, no changes in Stroop-related BOLD responses were seen following treatment (contrast of post- versus pre-treatment; $pFWE>.05$).

3.4. Baseline fMRI and relationship to clinical variables

Findings from regression analyses related to pretreatment fMRI data and baseline clinical variables are shown in Table 2. Significant positive associations between pretreatment BOLD responses during incongruent versus congruent trials (Stroop effect) and pre-treatment MNWS scores were observed within bilateral IFG, Acc and right VS ROIs ($pFWE<.05$). These associations remained significant even after controlling for behavioral Stroop performance measures (RTs) and baseline cotinine levels ($p's<.05$). No significant associations between BOLD responses during incongruent versus congruent trials (Stroop effect) and baseline cotinine levels were observed within the *a priori* ROIs.

3.5. Intra-individual changes in BOLD response and abstinence during treatment

Regression analyses indicated a significant negative association between changes in BOLD response (Stroop effect at post- versus pre-treatment) within the left Acc and percent days of abstinence during treatment ($t_{(df=1,12)}=5.39$, $pFWE=.020$; peak[x,y,z]=-3, 32, 2; Figure 2A). Changes in BOLD response within the right insula were significantly negatively associated with maximum durations of consecutive abstinence ($t_{(df=1,12)}=4.96$, $pFWE=.046$; peak[x,y,z]=45, -16, 5; Figure 2B). These findings remained significant after controlling for randomization group (e.g., NRT versus placebo), for behavioral performance measures (RTs, incongruent/congruent errors) and for baseline indices of smoking severity (cotinine levels and MNWS scores) ($p's > .01$). Post-hoc calculations indicated relatively robust effect sizes for regression analyses for the Acc (Cohen's d, effect-size $r = 3.11$, 0.84) and insula (Cohen's d, effect-size $r = 2.86$, 0.82).

4. DISCUSSION

This study tested the hypothesis of treatment-associated changes in neural activity during cognitive-control processes via analysis of pre- and post-treatment fMRI data from a sample of adolescent tobacco smokers. Neuroimaging data were acquired during performance of a widely used cognitive-control (Stroop) task previously used to detect treatment-associated neural changes in adults with substance addictions (Brewer et al., 2008; DeVito et al., 2012).

fMRI data were analyzed to determine whether baseline indices of smoking related to neural responses, whether participation in smoking-cessation treatment was associated with changes in neural responses, and whether individual differences in treatment-related neural changes related to differences in treatment outcomes. Study findings and clinical implications are discussed below.

4.1. Stroop-related neural responses and baseline measures

The Stroop task is a well-validated probe of ‘top-down’ cognitive-control circuitry and is further associated with activation of limbic reward regions in adolescents and adults (Potenza et al., 2003; Banich et al., 2007; Silveri et al., 2011; Worhunsky et al., 2013). Consistent with this, robust effects of Stroop-task performance on neural responses within the Acc, IFG, insula and VS (a priori ROIs) were seen at both pre- and post-treatment. At baseline (pre-treatment), neural responses within inhibitory control (Acc and insula) and reward regions (VS) were further positively associated with severities of nicotine-withdrawal symptoms (as assessed using the MNWS). By contrast, no associations between baseline cotinine levels and neural responses were observed within any of the *a priori* ROIs, suggesting that severity of subjective nicotine-withdrawal symptoms may be related to neural responses independent of acute nicotine levels. However, as recent data suggest that rate of nicotine clearance, as indexed using nicotine metabolite ratio (3'-hydroxycotinine/cotinine), is related to neural responses to smoking cues during early abstinence in adults (Falcone et al., 2016), further work into the relationship between baseline cotinine (and other nicotine metabolite) indices and BOLD responses in adolescence is warranted.

Associations between self-reported nicotine-withdrawal symptoms and neural responses remained significant after controlling for behavioral Stroop task performance, suggesting that higher subjective nicotine-withdrawal symptoms may be related to decreased efficiency of cognitive-control regions (as indicated by increased neural responses not attributable to behavioral performance differences; DeVito et al., 2012; Kozasa et al., 2012). Behavioral interventions targeting inhibitory control processes have been demonstrated to improve performance and reduce neural responses in adults (Hartmann et al., 2015). Further research is needed to determine whether this type of behavioral training could be efficacious in reducing subjective withdrawal symptoms in adolescents (via increased neural efficiency), and thus might be a beneficial addition to existing treatments.

4.2. Changes in neural responses

Based on findings from the adult literature (Culbertson et al., 2011; DeVito et al., 2012), we anticipated that participation in smoking cessation treatment would be associated with decreased BOLD responses, indicating increased efficiency of inhibitory control mechanisms (Kozasa et al., 2012). Contrary to this, no significant changes in Stroop-related neural activations were observed across time points when averaged across participants (group-level comparison). All of the adolescents included in these analyses completed the full six-week treatment. Although the sample size of participants completing both pre-and post-treatment scans was limited, the data suggest that treatment participation and reduction of smoking in this sample did not effect changes in neural responses related to cognitive control among adolescent smokers.

However, consistent with our second hypothesis, there was a significant association between intra-individual changes in neural responses and abstinence measures, such that individuals with greater reductions in BOLD signal within the Acc and insula had longer durations of abstinence during treatment. Both the Acc and insula are implicated in multiple processes relevant to tobacco-use behaviors, including craving, cue-reactivity and motivational self-control processes (Brody et al., 2004; Culbertson et al., 2011; Goldstein and Volkow, 2011; Naqvi et al., 2014; Janes et al., 2015). These regions have further been implicated in studies of smoking quit attempts in adults (Janes et al., 2010; Culbertson et al., 2011; Sweitzer et al., 2016) and in a prospective study of adolescent smokers (Krishnan-Sarin et al., 2013). However, this is the first study to demonstrate that changes over time in neural function of these regions are linked to abstinence in an adolescent population.

These findings may be interpreted several ways. It is possible that nicotine abstinence may result in increased neural efficiency, manifesting as decreased BOLD signal. In rats, acute nicotine administration is associated with increases in BOLD signal within regions including the insula and thalamus (Bruijnzeel et al., 2015). Thus, abstinence from nicotine might be hypothesized to decrease neural responses in these regions. Somewhat contrary to this, we found no evidence of an association between nicotine levels (as assessed using urinary cotinine) and BOLD responses at baseline. An alternative interpretation is that abstinence from tobacco may be dependent on changes in cognitive control-related neural responses. Within this context, individuals with increased neural efficiency during cognitive control might be more able to successfully inhibit smoking urges and thus achieve more days of abstinence. This interpretation is consistent with data indicating reductions in Stroop-related anterior cingulate activity following substance-use treatments among adults (DeVito et al., 2012), as well as with other data prospectively linking increased insular responses to relapse in adult tobacco smokers (Janes et al., 2010).

The majority of adolescents (~79%) included in pre- versus post-treatment comparisons received active NRT (versus placebo patch). While we controlled for this statistically in follow-up analyses, we cannot exclude the possibility that associations between changes in neural responses and abstinence measures may have been influenced by the NRT specifically. Further work with larger samples of adolescents with and without NRT is therefore warranted.

4.3. Future directions and conclusions

This preliminary study did not employ any network-based analyses, as in recent studies of adult smokers (Lerman et al., 2014). In adults, alterations in functional connectivity between the insula and Acc persisted even following prolonged abstinence in adult smokers (Zanchi et al., 2015), and increased functional connectivity between the insula and sensorimotor areas has been associated with favorable outcomes following a quit-attempt (Addicott et al., 2015). Thus, an important future direction will be to employ network-based analyses to identify network-level factors potentially related to smoking-cessation outcomes among youth.

This study has several additional limitations, including the absence of a control group. Inclusion of a matched control group of adolescent non-smokers would have allowed us to

control for possible test-retest effects on neural Stroop-related activations, which might have complicated interpretation of findings. However, on average, Stroop-related activations were consistent across time points (as evidenced by the absence of group-level changes). A further limitation of this study is the small sample size ($n=14$ for pre- versus post-treatment analyses) which prevented exploration of possible effects of specific treatments (e.g., CM for abstinence versus CM for attendance) on neural responses over time. These data therefore require replication using larger sample sizes and should be considered preliminary in nature. Given the small sample size, we were only powered to detect relatively large effects. Consistent with this, relatively robust effect sizes were observed for associations with treatment outcome measures. However, replication of these findings is still required. Further, as noted above, additional research is needed to disentangle the effects of acute abstinence from those of successful behavioral change (increased control of smoking behaviors) in relation to fMRI measures. This study also has several strengths, including the within-subjects design and the successful combination of fMRI scanning with a larger RCT conducted in a vulnerable and under-studied population.

To our knowledge, this is the first multiple time-point fMRI study of addictions treatment in an adolescent population. Our findings suggest that abstinence during smoking cessation treatment among adolescents is associated with increased neural efficiency of brain regions involved in cognitive control. Thus, appropriate engagement of these regions during cognitive-control processes may contribute to successful smoking-cessation outcomes in this population. Recent data indicate that both inhibitory-control training and more general working-memory training may be effective among adults with addictions (Bickel et al., 2011; McClure and Bickel, 2014; Wesley and Bickel, 2014; Hartmann et al., 2015). Taken together, our findings suggest that augmenting smoking-cessation treatments for adolescents with additional interventions specifically targeting neural efficiency of cognitive-control regions may be helpful in improving smoking-cessation rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The first multiple time-point fMRI study of addictions treatment in adolescents
- Reductions in cognitive-control related activity (anterior cingulate, insula) were associated with smoking abstinence during treatment

Figure 1.
Main effects of Stroop task performance (incongruent versus congruent trials) on neural responses among adolescent smokers at pre- and post treatment
Whole-brain findings, cluster-level corrected at $p_{FWE} < .05$ (voxel-level- $p < .001$). L=left; R=right

A. Association between change in anterior cingulate activity and percent days abstinent during smoking cessation treatment

B. Association between change in insula activity and maximum durations of consecutive abstinence during smoking cessation treatment

Figure 2.

Associations between changes in Stroop-related BOLD response (post-treatment versus baseline) and abstinence during smoking cessation treatment

Left: Individual clusters from uncorrected ($p < .01$) whole-brain analyses are shown for illustrative purposes. Right: Extracted signal from peak activations identified in small-volume-correction (SVC) regression analyses are plotted (10mm sphere) to illustrate associations with abstinence measures. L=left; R=right; μ =BOLD signal change

Table 1

Demographic and clinical characteristics of adolescent smokers scanned prior to randomization to smoking cessation treatment*

		Placebo (n=8)		Nicotine Patch (n=12)		x ²	p	df
		n	%	n	%			
Behavioral Tx	CM for Abstinence	3	37.5	5	41.7	0.15	0.697	1
	CM for Attendance	5	62.5	7	58.3			
Gender	Female	3	37.5	5	38.5	0.00	0.965	1
	Male	5	62.5	8	61.5			
Grade	9th	0	0.0	2	15.4	2.31	0.511	3
	10th	3	37.5	2	15.4			
	11th	2	25.0	4	30.8			
	12th	3	37.5	5	38.5			
		Mean	St. Dev	Mean	St. Dev	t	p	df
Age		16.75	1.28	17.15	1.35	-0.68	0.505	19
Baseline variables								
	Minnesota Nicotine Withdrawal Scale	11.25	7.54	12.82	5.31	-0.53	0.600	17
	Urinary cotinine	899.50	479.66	678.92	321.55	1.26	0.220	19
	Modified FTND	3.79	1.20	3.03	1.53	1.17	0.259	17
	Age started smoking daily	13.25	1.83	13.83	2.76	-0.52	0.607	18
	Cigarettes per day at smoking initiation ^a	12.38	23.45	8.42	7.68	0.55	0.590	18
	Current cigarettes per day (baseline) ^b	10.36	5.50	12.56	5.20	-0.889	0.386	17
Treatment variables								
	Days in treatment (out of 42)	21.75	18.48	42.00	0.00	-4.02	0.001	19
	Days abstinent during treatment (%)	83.33	13.04	68.50	32.21	0.98	0.340	16
	Maximum duration of consecutive abstinence (days)	21.00	11.94	17.54	11.22	0.58	0.572	16
	Cigarettes per day at end of treatment ^c	0.14	0.25	1.06	1.31	-1.53	0.148	15

* Demographic and clinical data for one individual who dropped out of the study subsequent to fMRI scanning but prior to randomization not included; CM=contingency management; St. Dev.=standard deviation; FTND=Fagerstrom Test for Nicotine Dependence

^a based on self-report from the Smoking History Inventory (SHI);

^b number of cigarettes per day (mean over one week) at baseline, as assessed using the Substance Use Calendar (SUC);

mean number of cigarettes per day reported during last week of treatment, as assessed using the Substance Use Calendar (SUC)

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Table 2

Associations between pretreatment BOLD response and baseline clinical variables

		Minnesota Nicotine Withdrawal Scale					Urine Cotinine Level				
		x	y	z	t	p	x	y	z	t	p
Anterior cingulate	R	3	17	26	3.88	0.014 *	15	20	26	2.06	0.633
	L	-18	41	11	4.05	0.007 *	-18	44	-4	2.19	0.537
Insula	R	39	-22	-7	3.39	0.074	39	-10	-7	1.95	0.756
	L	-36	5	14	3.10	0.158	-42	5	14	2.12	0.669
Inferior frontal gyrus	R	30	17	-19	4.31	0.009 *	48	17	11	2.56	0.613
	L	-33	8	-16	4.50	0.004 *	-36	26	5	2.36	0.749
Ventral striatum	R	9	5	-13	3.08	0.009 *	12	11	-7	1.08	0.346
	L	-9	5	-7	2.38	0.052	-12	11	-7	1.26	0.288

Family-wise-error (FWE) correction for multiple comparisons for each of the *a priori* regions of interest (ROIs) was conducted using small-volume-correction (SVC; pFWE<.05) in SPM12. ROIs are shown in Supplemental Figure 2.