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An Exploratory Pilot Study of the Relationship between Neural Correlates of Cognitive Control and Reduction in Cigarette Use among Treatment-Seeking Adolescent Smokers

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Abstract

Despite high rates of tobacco use during adolescence, few empirically validated smoking cessation strategies exist for adolescent smokers. Developing an understanding of the neural underpinnings of cognitive control processes in adolescent smokers, and their relationship to quit behaviors, may help advance the development of enhanced behavioral and pharmacological therapies. The current pilot study explored the relationship between brain responses during performance of the Stroop color-word interference task and reduction in tobacco use (as measured by changes in cotinine levels) in treatment-seeking adolescent smokers participating in a high-school-based smoking-cessation program. Eleven adolescent daily smokers participated in a pre-quit session during which neural activity in response to congruent and incongruent events in a Stroop task was examined using functional magnetic resonance imaging (fMRI). Changes in urine cotinine levels from pre-quit baseline to end of treatment were calculated and correlated with brain activity. Adolescents with greater activation in the inferior frontal gyrus, insula, thalamus and anterior cingulate had greater reductions in cotinine levels. The preliminary observation of a relationship between treatment outcome and neural correlates of cognitive control prior to treatment onset provides insight into individual differences in adolescent brain function that might relate importantly to treatment outcome.

Keywords

Adolescent; Stroop; cigarette; smoking; treatment

Introduction

Tobacco smoking, one of the leading precedents of a number of disease states and premature death, is primarily initiated during adolescence (Arrazola, Dube, Kaufmann, Caraballo, & Pechacek, 2011). According to the World Health Organization (WHO, 2013), if current trends continue, approximately 250 million children and teenagers who initiate smoking will die from tobacco-related diseases in adulthood. In the US alone, nearly 2000 children and adolescents begin smoking each year and more than 1/5th are current smokers by the time

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they leave high school. While most adolescent smokers report high interest in quitting smoking (61%; Arrazola et al., 2011), the success rates of aided and unaided quit attempts are low and range between 7–12%, and most existing treatments have limited success (Backinger & Leishchow, 2001; Grimshaw & Stanton, 2006; Sussman, 2002; Sussman, Ping, & Dent, 2006; Wiehe, Garrison, Christakis, Ebel, & Rivara, 2005). A better understanding of the neurobiological correlates of treatment outcome may facilitate the development of more effective cessation strategies.

Adolescence is a period of great developmental plasticity and growth, particularly in areas of the brain such as the prefrontal cortex that are important for higher executive functions governing cognitive control (Galvan, Hare, Parra, Penn, Voss, Glover & Casey, 2006; Giedd & Rappoport, 2010). Neural circuitry underlying cognitive control, a construct involving aspects of attention, conflict monitoring and response inhibition (Botvinick, Braver, Barch, Carter, & Cohen, 2001), has been proposed to contribute to decision-making underlying participation in addictive behaviors (Bechara, 2003). It has been proposed that during adolescence, differential neurodevelopmental trajectories of brain regions, and their interconnected circuitry, may enhance adolescent susceptibility to many high-risk behaviors, including tobacco use (Ernst, Romeo, & Andersen, 2009; Rutherford, Mayes, & Potenza, 2010; Somerville, Jones, & Casey, 2010; Chambers, Taylor, & Potenza, 2003). More specifically, tobacco use has been found to relate to deficits in neural circuitry underlying cognitive control and related processes (Galvan, Poldrack, Baker, Mcglennen, & London, 2011; Jacobsen, Slotkin, Mencl, Frost, & Pugh, 2007). Together, these data highlight the relevance of studying the neural circuitry underlying cognitive control in adolescents seeking to quit tobacco use.

This pilot study in treatment-seeking adolescent smokers is the first to explore the relationship between pre-treatment brain activation during performance of the Stroop color-word interference task and treatment-related changes in tobacco use. We chose to use the Stroop, a task that assesses cognitive control (Botvinick et al., 2001), because: 1) neural correlates of Stroop task performance have been previously investigated in adults (Peterson, Skudlarski, Gatenby, Zhang, Anderson, & Gore, 1999; Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000) and adolescents (Peterson, Potenza, Wang, Zhu, Martin, Marsh, Plessen, & Yu, 2009); and, 2) both behavioral (Streeter et al., 2007) and neural (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008) correlates of Stroop task performance have been linked to treatment outcomes amongst cocaine-dependent adults. In these last two studies, increased task-related activation of cortico-striatal brain regions including the ventromedial prefrontal cortex (vmPFC), cingulate cortex and striatum at treatment onset was associated with better abstinence at treatment outcome. Therefore, we hypothesized that amongst adolescent smokers pre-treatment activation of similar regions (vmPFC, cingulate and striatum) would correlate with decreases in biological measures of tobacco use. Furthermore, since the inferior frontal gyrus (IFG) has been shown to be associated with response inhibition in adolescents and adults across species (Galvan et a., 2011; Finnenberg et al., 2010), and the insula and dorsal anterior cingulate (ACC) have been linked to tobacco abstinence maintenance among adult smokers (Janes et al., 2010), we also hypothesized that Stroop-related activations in these regions would be associated with reductions in cotinine

levels (a metabolite of nicotine which has a longer half life of 18–20 hours compared with that of nicotine which is 2–3 hours).

Material and Methods

All study procedures were approved by the Yale School of Medicine Human Investigations committee. Prior to initiation of any study procedures, parental consent and adolescent assent was obtained from participants aged 14–17 years and consent was obtained from adolescents who were 18 years old.

Participants

Adolescent smokers were recruited from local Connecticut high schools to participate in a smoking cessation research study using procedures similar to our earlier work (Cavallo et al., 2007; Krishnan-Sarin et al., 2006). Adolescents had to report smoking at least five cigarettes per day for the past six months, with quantitative urine cotinine levels of 350 ng/ml or higher (Graham Massey Analytical Labs, Shelton, CT), and had to be seeking treatment. The participants in the current study (n=11) were a subgroup who chose to participate in the fMRI study from a larger group of 82 smokers who participated in a smoking cessation trial (Krishnan-Sarin et al., 2012) all of whom were offered the option of completing the fMRI study.

All participants completed questionnaires assessing demographic information, smoking history as well as nicotine dependence (modified Fagerstrom Tolerance Questionnaire; mFTQ; Prokhorov, Pallonen, Fava, Ding, & Niaura, 1996). The Diagnostic Interview Schedule Children Predictive Scale (DPS; Lucas et al., 2001) and an evaluation by a clinical psychologist were used to assess current DSM-IV Axis I disorders (First, Spitzer, Gibbon, & Williams, 2002) and exclude those with a current diagnosis of generalized anxiety disorder, major depressive disorder, or a substance dependence disorder (other than nicotine dependence). We also excluded those with any significant current medical condition, endorsing a suicidal/homicidal risk or using any psychotropic medications (including anxiolytics and antidepressants). Other exclusionary criteria included color-blindness or pregnancy and conditions that are contra-indicated to fMRI scanning.

fMRI Stroop Task

A week to ten days prior to initiating the treatment program, all participants performed the fMRI Stroop color-word interference task as described in the “supplemental materials” section and in our previous publications (Brewer et al., 2008; Devito, Worhunsky, Carroll, Rounsaville, Kober, & Potenza, 2012).

Smoking Cessation Intervention and Other Procedures

All interventions were guided and supervised using manuals based on our previous work (Cavallo et al., 2007; Krishnan-Sarin et al., 2006). Briefly, all participants scheduled a quit date which was the start of a four-week treatment period and received a 45-minute “preparation to quit” session, 4–7 days prior to their quit date, during which motivational and cognitive behavioral strategies were used to emphasize the risks of continued smoking

and benefits of quitting and teach strategies to initiate cigarette abstinence on quit day. At the end of this session, adolescents were randomly assigned to receive one of three treatment conditions for four weeks following quit date: Cognitive Behavioral Therapy (CBT) alone (no abstinence reinforcement), Contingent Reinforcement for abstinence (Contingency Management - CM) alone, or CBT+CM. Those in the CM conditions could receive up to $262 over the four weeks if they remained abstinent [as assessed daily using CO levels (Vitalograph Breath CO, Bedfont, MA0 and semiquantitative urine cotinine readings (NicAlert Immunoassay Test Strips, Jant Pharmacal Corporation, Encino, CA)]. All groups also received payments ($5–$20) for attending weekly assessment appointments and completing CBT sessions. Payments for attendance were chosen to ensure fairly equivalent total incentives across groups (and minimize the possibility of differences in outcome being related to incentive amounts) and were as follows: 1) CM alone group: $5 at each weekly appointment for completing assessments, 2) CM + CBT group: $5 at each weekly appointment for completing assessments and $5 for attending CBT sessions, 3) CBT alone group: $20 at each weekly appointment for completing assessments and $20 for attending CBT sessions.

Participants also received monetary compensation ($75) for completing the fMRI session. The primary outcome was end of treatment quantitative urine cotinine levels (Graham Massey Analytical labs, Shelton, CT).

Data Analyses - 2.4.1 fMRI Data Acquisition and Analyses

Images were obtained with a Siemens TIM Trio 3T MRI system (Siemens AG, Erlangen, Germany) and analyzed using methods described in our previous publications (Brewer et al., 2008;Devito et al., 2012; Kober et al., 2010) and in the “supplemental materials” section.

Changes in Cotinine Levels and Stroop-related Activity—Percent changes in cotinine levels were calculated by subtracting end-of-treatment cotinine levels from the baseline. Per guidelines provided by Mermelstein and colleagues (Mermelstein et al., 2002), the two non-completers were considered to be smoking and therefore have no changes in cotinine levels. Correlations between differences in blood-oxygen-level-dependent (BOLD) signal-change during incongruent versus congruent conditions and percent change in cotinine levels during treatment were assessed using voxel-wise correlational analyses across the whole brain, employing a family-wise-error correction.

Results

Participants

Participants were 11 treatment-seeking adolescents (4 female; 9 Caucasian, 1 Hispanic, 1 African American) with a mean age of 17 years (SD=1.12) (Table 1) participating in a school-based smoking-cessation trial (Krishnan-Sarin et al., 2012). When compared to the 71 adolescents who did not participate in the fMRI study, the 11 participating adolescents did not differ on number of cigarettes/day [14.1 (SD=5.2) versus 12.22 (SD=4.99)] or average modified Fagerstrom scores [5.4 (SD=1.2) versus 5.4 (SD=1.8)], but did have higher baseline urine cotinine levels [1315 (SD=786) versus 1091 (SD=205) ng/ml, $p<0.05$].

While none of the participants met criteria for any non-nicotine substance abuse or dependence, 6 reported marijuana use and 7 reported alcohol use (see Table 1). Of the 11 participants, eight completed the four-week intervention program, one quit but discontinued treatment after the first week and two discontinued treatment prior to quit day. There were no demographic differences between completers and non-completers, or in end-of-treatment cotinine levels between treatment modalities.

Cotinine Levels

End-of-treatment cotinine levels were significantly reduced in all completers from baseline levels of 1250 (SD=814) to 259 (SD=104) ng/ml ($t=3.18$, $p<0.05$), with three participants having levels of 0 ng/ml.

Stroop Behavioral Performance

A paired-samples t-test showed a significant difference in reaction times between congruent and incongruent stimuli ($t=-3.19$, $p=.01$). Average reaction time to congruent stimuli was significantly shorter (M=446.56msec, SD=90.57) than the average reaction time to incongruent stimuli (M=533.13msec, SD=169.19), consistent with greater interference during incongruent trials. The mean number of errors per incongruent Stroop run was 2.34 (SD=1.64), representing an overall error frequency of 6.7%. Behavioral measures (reaction times to congruent and incongruent stimuli and Stroop error rates) did not correlate with baseline smoking (mean cigarettes/day) or percent change in cotinine levels during treatment (both $p>0.05$).

fMRI Results

fMRI Stroop Effect—The main effect of Stroop trials is described in Table 2A. Consistent with other fMRI studies of the Stroop-effect (Carter & Van Veen, 2007), the contrast of incongruent versus congruent trials showed increased activity in areas including the bilateral IFG, insula, dorsal ACC, medial prefrontal cortex (mPFC) and subcortical regions including the striatum and thalamus (Supplemental Figure 1). Baseline levels of smoking (cigarettes/day, cotinine levels) correlated with Stroop-related activations (shown in “Supplemental Results” section).

Correlations Between Changes in Cotinine Levels and fMRI Stroop Effect—Whole-brain correlations were performed between percent change in cotinine levels from baseline to the end of study and pre-treatment Stroop activity (incongruent vs. congruent trials; Supplemental Figure 2; Figure 1; Table 2B). Percent change in cotinine levels was positively correlated with Stroop-effect activity in the: 1) right insula extending to the right IFG (Figure 1a); 2) dorsomedial frontal gyrus (Figure 1c) extending ventrally to the ACC (Figure 1b); and, 3) right midbrain extending to the thalamus (Supplemental Figure 2). Percent change in cotinine levels was negatively correlated with activation in the: 1) right superior frontal gyrus; and, 2) the posterior cingulate extending to the parahippocampal gyrus (Supplemental Figure 2).

Discussion

This pilot investigation examined the relationship between pre-treatment regional brain activation during a cognitive control task in treatment-seeking adolescent smokers. We observed that reduction in tobacco use, as measured by changes in urine cotinine levels, was related to pre-treatment Stroop-related brain activations. As in previous studies of adults and adolescents (Leung et al., 2000; Peterson et al., 2009, Devito et al., 2012; Worhunsky et al., 2013), fMRI Stroop effect was associated with activation of brain regions including dorsolateral prefrontal, ventrolateral prefrontal, insular and anterior cingulate cortices. Greater activation in the IFG, ACC and insula, but not in the vmPFC or striatum, was associated with greater reduction in cotinine levels (Brewer et al., 2008). Activity in other regions including dorsal mPFC, thalamus, posterior cingulate, cerebellum and parahippocampus was also related to treatment outcome. These preliminary results indicate that adolescents showing greater Stroop-related activation of cognitive control circuitry prior to behavioral therapy may be better able to decrease or quit their smoking. One attractive explanation for this finding is that they may be able to do so by more successfully exerting cognitive control in situations that might interfere with their quit effort. Alternatively, these activation patterns may reflect a greater capacity to incorporate elements of behavioral therapies and future studies (including pre-/post-treatment measurement powered to investigate each therapy) are needed to examine these possibilities.

The findings from the present pilot study show both similarities to and differences from findings from other drug-using populations. For example, although pre-treatment Stroop-related brain activation was related to better biologically measured treatment outcomes in the present study, different brain regions (the vmPFC, striatum and more posterior aspects of the cingulate) were implicated in a study of cocaine-dependent adults (Brewer et al., 2008). However, subsequent analysis of the cocaine-dependent adults using independent component analysis related activations of many of the brain regions identified in the current study (including dorsal ACC, mPFC, insula, IFG and thalamus) to networks linked to treatment outcome (Worhunsky et al., 2013). Additionally, increased activation of similar brain regions has been observed during performance of a cognitive control task in a separate study of cocaine-abusing adults and linked with treatment outcome (Connollya, Foxec, Nierenberge, Shpanerc, & Garavan, 2012), suggesting that these regions contribute to cognitive control and outcome more broadly.

Interestingly, amongst female adult smokers, relatively increased pre-treatment activation of the insula and dorsal ACC in response to smoking-related cues was observed in those who later slipped or relapsed to smoking (Janes et al., 2010). Furthermore, relatively diminished functional connectivity between the insula and ACC was observed in the slip/lapse group, and the degree of smoking-cue-related activation in the insula and ACC correlated with smoking-related attentional biases. These findings and others (Peterson et al., 1999; Janes et al., 2010; Wexler, 2001) suggest that some smokers might be better able to engage similar brain regions for attentional rather than motivational purposes when presented with smoking-related visual cues (Janes et al., 2010b). Thus, in the present study, relatively greater Stroop-related engagement of ACC and related neurocircuitry was implicated in attentional and impulse control aspects of Stroop performance (Petersen et al., 1999). These

results also suggest possible greater disengagement of regions like the posterior cingulate implicated in default mode processing. Both congruent and incongruent conditions were associated with relatively diminished activity in this network; however, significantly greater decreases were noted in the incongruent condition. In this way, better cognitive control may be linked to improved treatment outcome in adolescent smokers. These findings resonate with those from other studies of drug dependence in which relatively increased activation of attentional circuitry during cognitive control processing and relatively decreased activation of similar regions during reward processing are linked to better outcomes (Brewer et al., 2008; Jia et al., 2011), consistent with the notion that "top-down" and "bottom-up" processes may compete for recruitment of overlapping networks (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011). Although currently speculative, these hypotheses warrant further testing and consideration in development of behavioral and pharmacological treatments for smoking cessation. For example, from a psychosocial perspective, teaching adolescents how to attend to cues and control impulses both at the conscious and subconscious levels using cognitive remediation strategies may warrant examination (Janes et al., 2010; Wexler, 2011). From a pharmacological perspective, medications that alter the function of these brain regions may help with treatment of addictions (Potenza et al., 2011).

From a developmental perspective, preclinical evidence suggests that the frontal regions of the adolescent brain are particularly susceptible to nicotine, and that changes induced by nicotine exposure may lead to cognitive deficits that persist into adulthood (Counotte et al., 2008; Schochet, Kelley, & Landry, 2005). Clinical evidence from adult smokers supports the existence of cognitive deficits, especially in deprived smokers, and nicotine appears to increase task-related neural activity in deprived but not in active smokers (Newhouse, Potter, Dumas, & Thiel, 2011). In contrast, the influence of tobacco use and deprivation on cognitive deficits in adolescents is still controversial (Colby et al., 2010; Dinn, Aycicegi, & Harris, 2004; Jacobsen, Krystal, Mencl, Westerveld, Frost, & Pugh, 2005; Zack, Belsito, Scher, Eissenberg, & Corrigall, 2001). However, limited existing evidence suggests that adolescent tobacco users have deficits in the neural circuitry related to attention and memory processes (Jacobsen et al., 2007) as well as in executive-function-related processes (Galvan et al., 2011). We observed that during incongruent relative to congruent trials adolescent smokers experienced enhanced activity in frontal regions like the bilateral IFG, dorsal ACC, mPFC and subcortical regions including the striatum and thalamus. Since our study did not include nonsmokers, we cannot draw any conclusions about tobacco-specific deficits in neural responses on the Stroop task. However, Galvan and colleagues (2011) have reported that while adolescent smokers and nonsmokers did not differ in neural responses to a Stop-Signal task, heavier smoking was associated with greater cortical activation. It is important to note that adolescent smokers in our study were not deprived from cigarettes for a prolonged period of time, suggesting that effects observed were probably not related to nicotine abstinence. Future studies should examine the influence of tobacco smoking and abstinence on cognitive control processes and their neural underpinnings in adolescent smokers.

An important limitation of our study is the small sample size; thus conclusions should be drawn tentatively. Future studies with larger samples may replicate these findings or have greater power to detect efficacies related to specific individual characteristics or therapeutic

influences. Because of the limited sample size, we were unable to examine the effects of the different treatment modalities being tested in our intervention or examine fully relationships with other tobacco use parameters. Neural mechanisms underlying the efficacies of specific therapies have been proposed (e.g., see Feldstein-Ewing et al, 2011 for proposed neural mechanisms underlying motivational interventions), and the current study lays the foundation for similar studies investigating CBT and CM in youth. We did not collect any developmental variables (e.g. measures of pubertal maturation) and were therefore not able to examine developmental differences in responses. We also did not consistently obtain self-reports or biochemical tests of tobacco or other substance use immediately prior to the scan. Future studies need to control such potential confounding variables. Furthermore, while this small sample precluded meaningful investigation of potential influences of other substances, larger samples could allow for analyses that investigate directly the relationships with other measures of substance use, as we have done in other samples (Yip et al., 2013). Despite these limitations, a significant strength of our study is the inclusion of a well-characterized sample of adolescent smokers and the use of biochemical measures to evaluate reduction in tobacco use.

In summary, this exploratory and preliminary investigation suggests that adolescent smokers who exhibited at treatment onset greater Stroop-related activation in brain regions implicated in cognitive control were more successful at reducing tobacco use. Future studies should replicate these results in larger samples, examine the concurrent influence of variations in smoking levels and investigate directly the neural mechanisms underlying the efficacies of specific behavioral therapies. Neuroimaging research is typically challenging to conduct in adolescents, and this preliminary study provides initial novel, informative, proof-of-concept data that contribute importantly as a “next step” in the process of understanding the neural correlates of behavioral treatments for adolescent smokers. By continuing and expanding upon this line of research, it is anticipated that behavioral therapies may be refined and targeted through an improved understanding of how behavioral interventions change brain function and lead to diminishment or cessation of addictive behaviors in adolescents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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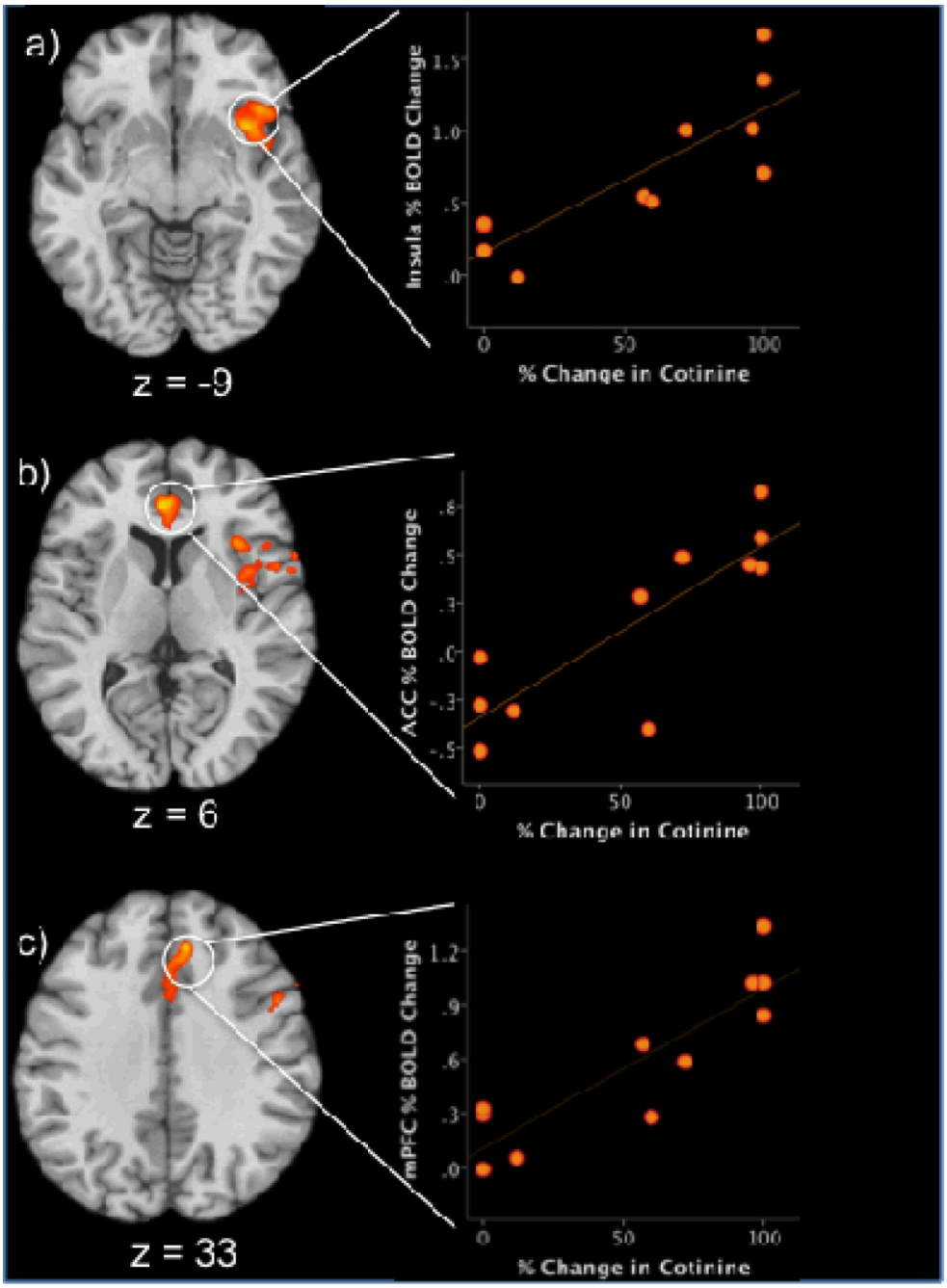

Figure 1.

Significant correlations between Stroop related activation and percent changes in cotinine levels (left side of figure). Orange/yellow indicates areas of positive correlations between % decrease in cotinine levels and increased % BOLD signal changes in the incongruent versus congruent contrast. Axial slices demonstrate the correlation with a cluster in the right insula (z=−9), ACC (z=6) and dorsal mPFC (z=33). Numbers indicate z-axis MNI coordinates. Right side of the brain is on the right. Scatterplots (right side of figure) demonstrate the distribution of individual scores in the correlation between % change in cotinine levels and

% BOLD signal change in A) Insula, B) ACC, and C) medal prefrontal cortex, during Stroop task performance in the adolescent smoking group (n = 11).

BOLD = blood-oxygenation-level-dependent

MNI = Montreal Neurological Institute

ACC=anterior cingulate cortex

mPFC= medial prefrontal cortex

r = Pearson correlation coefficient

Table 1

Characteristics of Adolescent participants

	Full sample	**CBT alone**	**CM alone**	**CM+CBT**
N	11	4	3	4
Male/Female	7/4	2/2	2/1	3/1
Age (SD)	17.0 (1.1)	16.5 (1.5)	17.0 (0.9)	17.5 (1.2)
Cigarettes/day	12.22 (4.99)	12.8 (4.0)	11.8 (3.5)	12.0 (5.0)
Baseline Cotinine	1315 (786)	1280 (450)	1340 (834)	1325 (720)
Fagerstrom scores	5.4 (1.8)	5.2 (2.5)	5.6 (1.1)	5.4 (1.5)
Marijuana use	N=6 10.8 (7.1) days/past month [0.5 joints/each day of use]	N=2 10.2 (4.3) days/past month	N=2 11.5 (8.5) days/past month	N=2 10.7(6.8) days/past month
Alcohol use	N=7 1.7 (0.9) days/past month [4.2 (0.3) drinks/drinking day]	N=3 1.8 (1.1) days/past month	N=1 1.6 days/past month	N=3 1.7 (0.9) days/past month
Treatment Completers	N=8	N=3	N=2	N=3

Table 2

A: Main effects (incongruent versus congruent stimuli) on the Stroop Task

Stroop Main Effect Contrast	Structure	BA	Left/ Right	MNI Coordinates x	y	z	k	T
Incongruent> Congruent	Anterior Cingulate/ Insula/Caudate/Thalamus/ Middle Frontal Gyrus	32	L	0	27	36	4536	13.03
	Inferior Parietal Lobule/ Supramarginal Gyrus	40	R	45	−30	51	979	10.67
	Inferior Frontal Gyrus/ Middle Frontal Gyrus		R	45	27	−3	1587	10.33
	Inferior Parietal Lobule	40	L	−51	−39	27	724	8.66
	Superior Frontal Gyrus/ Orbital Gyrus/ Medial Frontal Gyrus	8	L	−18	36	48	1883	−11.45
	Posterior Cingulate/ Middle Temporal Gyrus/ Precentral Gyrus/ Paracentral Lobule/ Postcentral Gyrus	23	L	−9	−57	12	2669	−9.36
	Middle Temporal Gyrus	21	L	−51	9	−27	447	−7.19
	Superior Temporal Gyrus	22	R	69	−27	6	460	−5.03

B: Stroop main effect correlations with percent change in cotinine levels

Stroop Main Effect Contrast	Structure	BA	Left/ Right	MNI Coordinates x	y	z	k	Peak R-value
Incongruent> Congruent	Medial Frontal Gyrus/ Anterior Cingulate/ vmPFC	9	R	9	36	33	280	0.886
	Insula/ Inferior Frontal Gyrus	13	R	6	−18	−15	298	0.857

BA = Brodman's Area
ROI = Region of Interest
k = cluster size in voxels
positive T values indicate regions in which greater activation is seen in response to incongruent versus congruent stimuli; negative T values indicate regions in which greater activation is seen in response to congruent versus incongruent stimuli

BA = Brodman's Area
ROI = Region of Interest
k = cluster size in voxels
vmPFC= ventromedial prefrontal cortex