Drug and Alcohol Dependence 167 (2016) 182–189

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Full length article

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

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ARTICLE INFO

Article history:
Received 3 May 2016
Received in revised form 5 August 2016
Accepted 15 August 2016
Available online 21 August 2016

Keywords:
Cigarette
Smoking
Young adult
Nicotine patch
Development
Quit attempt

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 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 ($pFWE < 0.05$). 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 ($pFWE < 0.05$).
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.

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)

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http://dx.doi.org/10.1016/j.drugalcdep.2016.08.019
0376-8716/

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 is 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 buproprion 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 related 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 that 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 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 Fig. 1.

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