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Short communication

Insula reactivity to negative stimuli is associated with daily cigarette use: A preliminary investigation using the Human Connectome Database

N.R. Dias[a,b,1], A.L. Peechatka[a,c,1], A.C. Janes[a,b,*]

[a] McLean Neuroimaging Center, McLean Hospital, Belmont, MA, USA
[b] Department of Psychiatry, Harvard Medical School, Belmont, MA, USA
[c] Suffolk University, Boston, MA, USA

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ABSTRACT

Background: Individuals who smoke more cigarettes per day are at greater risk for developing smoking-related illness and have more difficulty quitting. Withdrawal-related negative mood is one factor thought to motivate drug use. However, heavy smokers are generally more sensitive to negative affect, not just negative emotion stemming from withdrawal. One possibility is that individual differences in how the brain processes negative stimuli may impact smoking use. Given the wealth of data implicating the insula in nicotine dependence and affective processing we hypothesize that the number of cigarettes an individual smokes per day will relate to insula reactivity to negative stimuli.
Methods: A functional magnetic resonance imaging (fMRI) emotional processing task collected by the Human Connectome Project was assessed in 21 daily tobacco smokers who reported smoking between 5 and 20 cigarettes per day. The number of cigarettes smoked per day was correlated with right and left anterior insula reactivity to faces expressing a negative emotion relative to a control. This anterior insula region of interest has been associated with treatment outcome and smoking cue-reactivity in our prior work.
Results: Those who smoked more daily cigarettes showed greater right insula reactivity to negative stimuli ($r = 0.564$, $p = 0.008$). Left insula reactivity was not associated with cigarettes smoked per day.
Conclusion: Smokers who use more cigarettes per day have greater insula reactivity to negative stimuli, furthering the field's understanding of the insula's involvement in nicotine use. This preliminary work also suggests a mechanism contributing to higher rates of daily smoking.

1. Introduction

Over 36 million adults in the United States smoke cigarettes daily (Centers for Disease Control and Prevention (CDC), 2010), yet the number of cigarettes smoked/day varies across individuals (Shiffman, 2009; Burns et al., 1997). Understanding factors influencing smoking rates is essential, as greater smoking rates are associated with increased risk of smoking related illness (Bjartveit and Tverdal, 2005; Law and Wald, 2003) and with poorer quit outcomes (Harris et al., 2004; Hymowitz et al., 1997).

One factor possibly mediating daily cigarette use is reactivity to negative affect, as smoking is often maintained to alleviate negative mood states (Copeland et al., 1995; Brandon, 1994; Baker et al., 2004). Smokers self-administer greater numbers of cigarettes/day when faced with exogenous stressors (Aronson et al., 2008) and more rapid relapse is associated with decreased distress tolerance (Brown et al., 2002), suggesting that smoking may be related to how an individual processes negative affect. To test the hypothesis that daily smoking rates are associated with how negative affect is processed, we evaluated the relationship between the number of cigarettes an individual smokes/day and insula reactivity to negative stimuli.

Insula reactivity to negative stimuli in smokers is of particular interest, because this brain region is implicated in affective processing (Critchley, 2002; Critchley et al., 2004; Damasio et al., 2000; Phan et al., 2002; Craig, 2002, 2010) and smoking (Janes et al., 2010a,b; Naqvi et al., 2007; Gray and Critchley, 2007). The insula

* Corresponding author at: McLean Neuroimaging Center, McLean Hospital, 115 Mill St., Belmont, MA 02478, USA.
E-mail address: ajanes@mclean.harvard.edu (A.C. Janes).
[1] Authors contributed equally to this work.

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is engaged during the processing of basic affective states, including the interpretation of external stimuli such as emotional faces (Carr et al., 2003) and internal awareness of one's emotions (Critchley, 2002; Critchley et al., 2004; Damasio et al., 2000; Craig, 2002, 2010). Additionally, the insula facilitates nicotine seeking-behavior (Naqvi et al., 2007; Forget et al., 2010; Scott and Hiroi, 2011; Pushparaj et al., 2013) and is related to factors that impact daily smoking such as cigarette craving (Brody et al., 2002; Wang et al., 2007) and nicotine dependence severity (Claus et al., 2013). Thus, our analysis focused on a previously identified anterior insula region of interest (ROI) that is associated with smoking (Janes et al., 2015).

To identify an association between daily cigarette use and insula reactivity to negative stimuli, we investigated data collected via the Human Connectome Project (HCP; Van Essen et al., 2013). Specifically, we assessed whether the number of cigarettes smoked/day was correlated with insula activity collected during an emotional processing task where individuals were presented with faces expressing negative emotion compared to a neutral control. Given the insula's involvement in both emotional processing and nicotine dependence, we hypothesize that insula reactivity to negative stimuli will be associated with greater daily nicotine use.

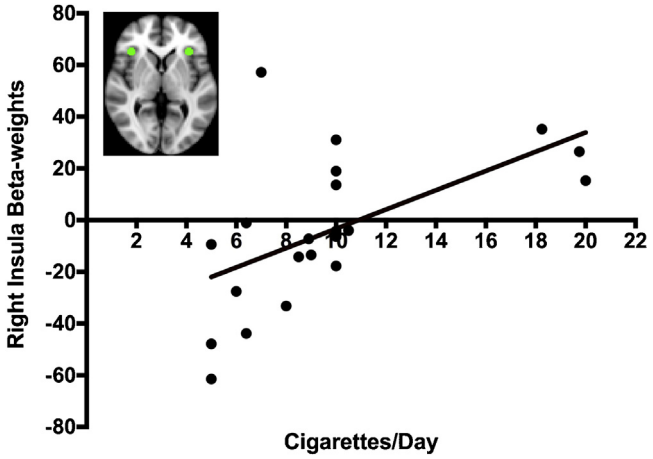

Fig. 1. Right insula activation: Negative faces > shapes. There is a positive relationship between right insula beta-weights for the negative faces > shapes contrast and the average number of cigarettes smoked per day (Pearson's $r = 0.564$, $p = 0.008$). The brain image on the top left shows the right and left insula ROIs in green.

2. Methods

2.1. Participants

Data analyzed were obtained from the Human Connectome Project (HCP). A description of the recruitment criteria for the HCP is provided by Van Essen et al. (2013). Briefly, individuals were excluded by the HCP if they reported a significant history of psychiatric disorder, substance abuse, neurological disorder, or medical disorder known to influence brain function. Participants in the current study included all those reporting regular cigarette use who did not have a positive urine sample indicating any illicit drug use or a history of alcohol or marijuana dependence. Twenty-one tobacco smokers (16 women, 2 left-handed) between the ages of 28 and 36 (mean = 30.3 ± 3.3 years) with an average of 13 years of education (±4.4) were assessed. All subjects reported smoking an average of 9.7 cigarettes/day (±4.4; range: 5–20), had an average nicotine dependence level of 3.14 ± 1.8 as measured by the Fagerstrom Test for Nicotine Dependence (FTND, Heatherton et al., 1991), and were abstinent for at least 1 h prior to the fMRI task.

2.2. fMRI data acquisition

All imaging data were acquired with a 32-channel head coil on a modified 3T Siemens Skyra. Uğurbil et al. (2013) provides a detailed description of the Human Connectome Project (HCP) fMRI acquisition protocols, which is summarized by Barch et al. (2013).

2.3. fMRI data preprocessing

The "minimally preprocessed" Quarter 3 release of the HCP data was used for this study (40). We further preprocessed these data using tools from FSL 5.0.6 (FMRIB Software Library; Analysis Group, FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl). Data were spatially smoothed to 4 mm full width half max and high pass temporal filter was applied (Gaussian-weighted least squares straight line fitting, with sigma = 100 s).

2.4. Experimental task design

The emotional processing task used by the HCP was adapted from a well-validated task developed by Hariri et al. (2012). Two 2 min and 5 s runs of the task were acquired. Each of the two runs began with an 8 s fixation, followed by 6 alternating blocks: three blocks presented face stimuli (angry or fearful faces) and the other three blocks presented shape stimuli (wide or tall circles). Prior to each block, a cue indicating the type of block (shape or face) was shown for 3 s. Each block lasted 18 s, in which six 2 s trials were followed by a 1 s inter-trial-interval. There was a bug in the E-prime script for this task, such that the task stopped short of the last three trials of the last block (face) in each run. As described on the HCP website (http://www.humanconnectome.org/documentation/Q1/task-fMRI-protocol-details.html), the last block of each run lasted only 9 s, which limited trial presentation of that face block to 3 face trials.

2.5. fMRI data analysis

At the first level, two regressors, one corresponding to emotional faces block and the other to shapes block, were included in the general linear model. These regressors were constructed using boxcar functions of length equal to the duration of the block and convolved with the double gamma hemodynamic response function. Motion was modeled using the six motion regressors (x, y, z, translation and rotation). First-level results were combined across runs and insula ROIs were subsequently extracted for each participant. A Pearson's correlation coefficient was calculated between the number of cigarettes smoked per day and right and left insula reactivity to negative faces > shapes. Anterior insula regions of interest were comprised of 5-mm spheres located at MNI coordinates (±34, 26, 2; x, y, z; Fig. 1), which are identical to the ROIs we used previously (Janes et al., 2015). To test the specificity of the anterior insula's involvement, we evaluated the relationship between cigarettes/day and the right and left mid (±8, 2, 2) and posterior insula (±38, −14, 8); ROIs, also taken from our prior work (Janes et al., 2015). To ensure that findings were not unduly affected by possible outliers, correlations were confirmed using Spearman's nonparametric test.

3. Results

3.1. Association between Insula reactivity and cigarettes/day

There was a positive association between cigarettes smoked/day and reactivity to negative faces > shapes in the right (Pearson's $r = 0.564$, $p = 0.008$; Fig. 1), but not left anterior insula (Pearson's $r = 0.253$, $p = 0.268$). This finding was supported by non-parametric testing using Spearman's rho (right anterior insula $r = 0.653$, $p = 0.001$). While there was a marginal association between cigarettes smoked/day and beta weights extracted from the right posterior insula (Pearson's $r = 0.446$, $p = 0.43$), this association was not significant when testing with Spearman's rho suggesting outliers were impacting this finding. No relationship was found between cigarettes smoked/day and any other ROI. No relationship was found between age and any ROI.

4. Discussion

Negative affect is associated with nicotine use (Kassel et al., 2003; Hughes et al., 1994), as ameliorating withdrawal-related negative affect is one of the most cited reasons for precipitating relapse (Copeland et al., 1995; Brandon, 1994; Baker et al., 2004). The current finding expands our understanding of the link between negative affect and daily cigarette use by demonstrating that right anterior insula reactivity to negative stimuli is positively correlated with cigarettes smoked/day.

While the bilateral (Naqvi et al., 2007; Janes et al., 2010b) and left insula (Engelmann et al., 2012; Janes et al., 2013) have been implicated in aspects of nicotine dependence such as reactivity to and memory for smoking cues, our finding that right insula activ-

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