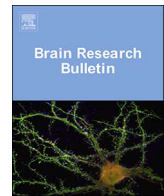




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## Changes in resting state functional brain connectivity and withdrawal symptoms are associated with acute electronic cigarette use

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### ABSTRACT

Resting state functional brain connectivity (rsFC) may be an important neuromarker of smoking behavior. Prior research has shown, among cigarette smokers, that nicotine administration alters rsFC within frontal and parietal cortices involved in executive control, as well as striatal regions that drive reward processing. These changes in rsFC have been associated with reductions in withdrawal symptom severity. We currently have a limited understanding of how rsFC is affected by the use of electronic cigarettes (ecigs), an increasingly popular class of products, the members of which deliver nicotine with varying effectiveness. The current study used fMRI to determine the effects of ecig use on rsFC and withdrawal symptoms. Independent component, dual regression, and permutation analyses were conducted on rsFC collected from ecig users before and after an ecig use episode ( $n = 9$ ) that occurred after 14 h of nicotine abstinence. Similar to the known effects of nicotine administration, ecig use decreased rsFC of two clusters in the right frontal pole and frontal medial cortex with an attentional control salience network, and decreased rsFC of five clusters in the left thalamus, insula, and brain stem with a reward network encompassing the striatum. Ecig use increased inverse coupling between the prefrontal reward network and the right frontoparietal executive control network. Reductions in craving and difficulty with concentration were correlated with decreases in coupling strength between reward and executive control networks. These preliminary results suggest that the effects of ecig use on rsFC are similar to those seen with nicotine administration in other forms. In order to gain insight into the addictive potential of ecigs, further research is needed to understand the neural influence of ecigs across the range of nicotine delivery within this class of products.

### 1. Introduction

Electronic cigarettes (ecigs) have grown in popularity in the U.S. over the past decade, especially among youth (Department of Health and Human Services, 2016; King et al., 2014). These devices use an electrical heating element to turn a liquid that typically contains propylene glycol, glycerin, nicotine and flavorants into an aerosol (Breland et al., 2016). Their popularity has been aided by marketing campaigns portraying them as a cigarette substitute, often implying the potential to serve as a safer alternative to combustible cigarettes or a stepping stone to cessation (Grana et al., 2014). However, some non-

smokers also report using ecigs, especially young adults under the age of 24 (Department of Health and Human Services, 2016). Despite concerns about ecig use leading to nicotine addiction, the prevalence of daily ecig use among 18–24 year-olds is estimated at 1.3%, which is low relative to the rates of cigarette smoking (14.7%) for this age group (Kasza et al., 2017). The FDA gained authority to regulate the manufacture and sale of ecigs in 2016, but we still know little about the safety and addictive potential of these products.

Acute and chronic nicotine use is associated with neural changes in midbrain and cortical areas involved in reward processing, motivation, learning, and executive functions (Engelmann et al., 2012; Kenny and

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Markou, 2006; McClernon et al., 2009). These changes can lead to the development of addiction and continued cigarette use despite physical harm (McLaughlin et al., 2015). Withdrawal symptoms, such as craving, anxiety, irritability, and negative affect, make nicotine abstinence difficult, and have neural correlates identified with functional magnetic resonance imaging (fMRI) (Buhler et al., 2010; Lerman et al., 2014; McClernon et al., 2008; McLaughlin et al., 2015; Mendrek et al., 2006). fMRI is a non-invasive brain imaging technique that measures changes in blood-oxygen-level-dependent (BOLD) neural activity over time. If ecigs produce similar effects on the brain as combustible nicotine products, this would imply that what we have learned about the neurocognitive effects of cigarette smoking will likely also apply to ecig use. However, we know little about how ecigs affect neural function, which is difficult to predict given the varying nicotine contents in the liquids and the power output (wattage) of the devices (Breland et al., 2016; Marsot and Simon, 2016).

Our prior investigation using fMRI showed that viewing images of ecigs elicits BOLD cue-reactivity in daily ecig users (Nichols et al., 2016). The effects of the ecig cue task, localized in sensorimotor cortical regions, were similar to cue-induced reactivity seen among daily smokers when viewing pictures of cigarettes (Engelmann et al., 2012; Nichols et al., 2016). fMRI is also used to measure associations between spontaneous fluctuations in BOLD signal throughout the brain when a person is not engaged in a goal-directed task, called resting state functional connectivity (rsFC) (Laird et al., 2011). Whole-brain networks of correlated rsFC have been linked to behavior relevant to addictive processes (Laird et al., 2011; Sutherland et al., 2012). Common networks include those that drive attention to external and internal stimuli to perform executive functions (e.g., frontoparietal, salience, and default mode networks), the visuospatial processing of complex numerical and emotional stimuli, and networks involved in evaluating and responding to reward (e.g. striatal and prefrontal networks) (Laird et al., 2011). RsFC has been shown to be altered among dependent smokers and predictive of relapse during quit attempts (Addicott et al., 2015; Fedota and Stein, 2015; Lerman et al., 2014; Sutherland et al., 2013; Sweitzer et al., 2016; Wang et al., 2016; Wetherill et al., 2015). When compared to non-smokers, daily smokers who are nicotine satiated show reduced rsFC of limbic, insular, and prefrontal cortical circuitry involved in reward processing, increased coupling strength between prefrontal and parietal cortical circuitry, and decreased coupling strength between insular and frontal cortical circuitry involved in executive functions (Bi et al., 2016; Fedota et al., 2016; Janes et al., 2012; Shen et al., 2016; Yuan et al., 2016).

After a period of nicotine abstinence, rsFC changes in response to nicotine administration via smoking, patch, and lozenge (Cole et al., 2010; Ding and Lee, 2013; Hong et al., 2009). For daily smokers, smoking after a 12-h period of abstinence was related to reductions in coupling strength between the default mode and salience networks, as well as enhanced coupling strength between the salience network with the combined frontoparietal and default mode networks (Ding and Lee, 2013). Enhanced rsFC between cingulate-cortical regions has also been noted with nicotine patch administration among daily smokers (Hong et al., 2009). In a separate study, daily smokers who had abstained from nicotine for 8 h showed reductions in rsFC in the salience network (i.e., insula, orbitofrontal cortex) and the default mode network (i.e., precuneus and cuneus) after being administered two doses of a 4 mg nicotine lozenge as compared to when they were administered a placebo lozenge (Cole et al., 2010). Changes in rsFC were associated with changes in withdrawal symptoms (i.e., craving, concentration, restlessness, and hunger): Specifically, reductions in total withdrawal symptoms were related to nicotine-induced increases in rsFC within the default mode (prefrontal, occipital, parietal, and hippocampal regions) and salience networks (prefrontal cortex), as well as decreases in temporal and occipital regions of the salience network. Nicotine-induced reductions in coupling strength between the salience and default mode networks were associated with fewer difficulties with

concentration after satiety (Cole et al., 2010). These results suggest that while nicotine may produce overall reductions in rsFC, withdrawal symptoms may be driven by more complicated network dynamics that include increases and decreases in network rsFC, as well as changes in connectivity strength between networks.

If nicotine is the mechanism driving these changes, one could expect to see similar changes in rsFC connectivity with nicotine administration via ecig use; however, given the lack of testing and regulations regarding nicotine delivery with these devices, their effects on neural processes remain unclear. The current study aimed to use a similar data-driven, whole-network approach as Cole et al. (2010) to identify anatomical locations of significant within-subject changes in rsFC induced by using an ecig after a 14-h period of nicotine abstinence among regular ecig users. We also assessed for associations between changes in rsFC with changes in withdrawal symptoms and blood nicotine levels measured during the ecig use episode. We expected to observe changes in rsFC similar those reported with other forms of nicotine administration, including decreased rsFC and reduced between-network coupling among executive and reward networks after ecig use.

## 2. Materials and methods

### 2.1. Participants

Participants were recruited from an online anonymous survey posted on websites and ecig forums that asked about smoking history, ecig use, and device preference. The survey was described previously in (Foulds et al., 2015) and (Yingst et al., 2015). Participants interested in research participation provided their contact information and those who lived locally were contacted and screened via phone for eligibility for the fMRI study. Eligible participants were between the ages of 18 and 60, used an ecig for at least 20 days out of the last 28 with a nicotine concentration in their ecig liquid of at least 12 mg/mL. Participants were excluded if they reported a chronic health condition (e.g., diabetes, hypertension, cancer), or cardiovascular or respiratory illness, current psychopathology or prescribed psychiatric medication, current drug or alcohol abuse, current pregnancy, difficulty donating blood in the past, or other safety MRI contraindications (e.g., metal fragments or implants). Eleven eligible participants completed MRI scans: One participant was excluded for incomplete data collection and another for excessive head motion during scanning. Data were collected across two research labs on Penn State University campuses (Hershey and University Park, PA) from May 2014 to April 2015. All participants provided informed consent prior to participation.

### 2.2. Procedures

Ecig users completed resting state fMRI scans before and after a use episode with their own ecig device. This strategy allowed for a comparison of rsFC while nicotine abstinent and after ecig use. Participants were asked to abstain from combustible cigarettes 4-days prior to the study visit (verified by carbon monoxide sample < 8 parts per million) and all nicotine and caffeine products 14 h prior to the study visit. Participants first completed a series of questionnaires on demographic, smoking history, and the 10-item Penn State Electronic Cigarette Dependence Index questionnaire (PSECDI) (Foulds et al., 2015). Directly after the first scan, participants responded to 24 computerized visual analogue scale (VAS) items regarding their withdrawal symptoms (e.g., “Please respond to each word or phrase with how you feel RIGHT NOW”) by clicking on a horizontal line ranging from “0-Not at all” to “100-Very much” for each withdrawal symptom (e.g., “difficulty concentrating”). Participants were then instructed to take one puff from their own ecig every 20 s for 10 min for a total of 30 puffs. Nursing staff sampled blood periodically during and after the use episode from a catheter inserted prior to the session. After removing the

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