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Neural correlates of graphic cigarette warning labels predict smoking cessation relapse

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ABSTRACT

Exposure to graphic warning labels (GWLs) on cigarette packaging has been found to produce heightened activity in brain regions central to emotional processing and higher-order cognitive processes. The current study extends this literature by using functional magnetic resonance imaging (fMRI) to investigate neural activation in response to GWLs and use it to predict relapse in an evidence-based smoking cessation treatment program. Participants were 48 treatment-seeking nicotine-dependent smokers who completed an fMRI paradigm in which they were exposed to GWLs, text-only warning labels (TOLs), and matched control stimuli. Subsequently, they enrolled in smoking cessation treatment and their smoking behavior was monitored. Activation in bilateral amygdala, right dorsolateral prefrontal cortex, right inferior frontal gyrus, left medial temporal gyrus, bilateral occipital lobe, and bilateral fusiform gyrus was greater during GWLs than TOLs. Neural response in the ventromedial prefrontal cortex (vmPFC) during exposure to GWLs (relative to a visual control image) predicted relapse during treatment beyond baseline demographic and dependence severity, but response in the amygdala to GWLs did not. These findings suggest that neurocognitive processes in the vmPFC may be critical to understanding how GWL's induce behavior change and may be useful as a predictor of smoking cessation treatment prognosis.

1. Introduction

There have been efforts to reduce the health burden of smoking through a variety of approaches. One such approach has been the use of warning labels on cigarette packages as a means of encouraging smokers to quit and deterring non-smokers from beginning to smoke (see Fig. 1). Epidemiological studies suggest that the introduction of these warnings was followed by reduced prevalence of smoking in Canada (Huang et al., 2014). Additionally, the Canadian graphic warning labels (GWLs) were demonstrated to decrease self-reported cigarette consumption and increase motivation to quit among smokers (Hammond et al., 2007, 2003). Studies have found that GWLs reduce overall craving (Emery et al., 2014; Wang et al., 2013) and demand for cigarettes (Thrasher et al., 2011). Furthermore, Wang and colleagues (Wang et al., 2015) found that viewing GWLs that were rated highly in emotional salience by participants reduced P300 amplitude response (a well-documented physiological marker of cigarette craving) to subsequent smoking cues. Additionally, research suggests that GWLs are more emotionally salient than text-only labels (TOLs) and may increase an individual's motivation to quit smoking (Kees et al., 2006). For example, one study found that GWLs induced greater self-reported motivation to quit smoking and higher fear intensity regarding the consequences of smoking than TOLs (Schneider et al., 2012). Another study found that GWLs elicited greater self-reported affective and cognitive reactions than TOLs (Nonnemaker et al., 2015).

Greater neural response in regions such as the amygdala, dorsolateral prefrontal cortex (dlPFC), insula, hippocampus, and inferior frontal gyrus has been specifically associated with GWLs to which participants report higher emotional reactivity (Wang et al., 2015). However, one region which seems to be especially important in understanding the neural response to GWLs is the ventromedial prefrontal cortex (vmPFC). The vmPFC is associated with many cognitive processes. It is also considered to be a part of the default network of the brain that is active during "rest", which is thought to consist primarily of mind wandering and self-directed thought (Andrews-Hanna et al., 2010, 2014). Related to this, it is considered

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Fig. 1. Examples of images shown in warning label paradigm. Panel A depicts a graphic warning label (GWL), panel B depicts a text only label (TOL), panel C depicts a scrambled image used as a visual control baseline.

a key region associated with self-referential thought (Denny et al., 2012; Falk et al., 2010, 2015).

The use of neuroimaging data to predict future behavior has been identified as a way that neuroscience can be applied pragmatically to improve individual outcomes (Gabrieli et al., 2015). As neuroimaging methods proliferate in medical centers around the U.S. and the world, using these methods to customize individual treatment plans becomes increasingly feasible (e.g., MRI and neuropsychological assessments are already comparable in price and travel distance). There are a number of ways that developing neural predictors of treatment outcome (termed "neuromarkers") may be utilized to improve quality of care. Neuromarkers may assist in customization of treatment plans in order to maximize the likelihood of patient success. For example, neural activity in the anterior cingulate cortex during a number of fMRI tasks predicts differential response to pharmacological and behavioral treatments for anxiety and depression (Ball et al., 2014). Neuromarkers may also be investigated in the context of novel neuropsychiatric treatments. For example, in depressed geriatric patients, fMRI response to a program of computerized brain training and physical exercise designed to enhance underactive neural systems (i.e., neuromarkers) was associated with a 90% rate of recovery over 4 weeks (Morimoto et al., 2014). Furthermore, neuromarkers can provide insight into the mechanisms of treatment. For instance, it has been shown that one putative treatment mechanism of motivational interviewing, *change talk,* is associated with reduced activation in several areas associated with reward and craving, underscoring the importance of facilitating change talk in alcohol use disorder treatment (Feldstein Ewing et al., 2011). These potential benefits suggest significant value in finding neuromarkers that may incrementally predict treatment prognosis beyond existing self-report and behavioral measures.

Increased vmPFC activity during health messages has repeatedly been shown to predict positive future health behaviors consistent with the message (Falk et al., 2012, 2011, 2010). Specific to cigarette smoking, one study that found that vmPFC activity in response to GWLs predicted population-level engagement with an online smoking cessation presentation (Falk et al., 2015). Most recently, a 2016 study showed that neural activation in the vmPFC and amygdala during GWLs predicted CO verified changes in smoking behavior over a two week period (Riddle et al., 2016). These results provide reason to believe that neural response to GWLs in the vmPFC and amygdala may be useful neuromarkers of smoking cessation treatment prognosis. However, since this study examined natural variations in smoking behavior and did not include smoking cessation treatment, it is unknown whether these regions would be useful as predictors of treatment outcome. Additionally, this study only tracked smoking for two weeks.

The goals of the current study were to investigate differences in neural activity in GWLs compared to TOLs and determine whether regions previously found to predict naturalistic change in smoking behavior (Falk et al., 2012; Riddle et al., 2016) predict success in a 9-week intensive smoking cessation treatment integrating pharmacological and behavioral components. Activation levels in the vmPFC and the amygdala during GWLs and TOLs (relative to a scrambled visual control image) were tested as predictors of the number of days until participants relapsed to smoking. We hypothesized that reductions in craving and increased activation in the vmPFC and amygdala during GWLs would be predictive of greater success (i.e., more days to relapse) in smoking cessation treatment.

2. Methods

2.1. Participants

Participants were recruited as part of a study on neuroimaging predictors of smoking cessation relapse. Participants all resided in the United States and as a result had limited prior exposure to GWLs since this type of warning is not currently used in the U.S. Participants were required to smoke at least 10 cigarettes per day and report a motivation to quit of at least 5 on a scale of 1–10. In order to avoid potentially confounding neurodevelopmental differences, participants were required to be right-handed and between 18 and 60 years of age. Participants were excluded for reporting major medical, neurological or psychiatric disorders based on a semi-structured interview administered at eligibility assessment visit. Other exclusionary criteria included reporting participation in smoking cessation treatment in the past 90 days, consumption of six or more alcoholic beverages per day, use of marijuana more than weekly, use of any other illicit drug more than monthly, or any MRI contraindications. Additionally, participants with an estimated IQ of less than 70 were excluded based on the Wechsler Test of Adult Reading (Holdnack, 2001); participants were of average general intelligence (final sample M=101.12, SD=14.85). Participants were paid $126 for participating in 5 experimental sessions and received free smoking cessation treatment. A total of 51 participants were enrolled and completed the fMRI assessment. Of these participants, 3 were excluded for excessive movement in the scanner (more than.35 mm moved during at least 33% of volumes collected). Thus, 48