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Individual differences in brain responses to cigarette-related cues and pleasant stimuli in young smokers

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ABSTRACT

Background: Decreased sensitivity to pleasant stimuli is associated with a higher vulnerability to nicotine dependence in youths and with difficulty quitting in adult smokers. Recently, we showed that smokers showing lower brain reactivity to non-cigarette-related pleasant images than to cigarette-related ones have lower chances of achieving long-term abstinence during a quit attempt.
Methods: We tested whether individual differences in brain responses to cigarette-related and pleasant stimuli require a long history of smoking to develop by measuring the late positive potential (LPP) to cigarette cues, emotional, and neutral stimuli in 45 young, light smokers (ages 18–25). *k*-means cluster analysis was used to partition smokers into two groups based on the magnitude of their LPPs.
Results: Group 1 was characterized by larger LPPs to pleasant pictures than cigarette-related pictures whereas Group 2 showed the opposite pattern.
Conclusions: Our results suggest that individual differences in brain responses to cigarette-related and pleasant cues do not require a long smoking history to develop.

1. Introduction

Chronic drug use is hypothesized to result in the attribution of excessive motivational value to drugs at the expense of natural rewards (Volkow et al., 2016, 2010). Recently, we found neurophysiological evidence to support this hypothesis in smokers using the late positive potential (LPP), an event-related potential (ERP) measure of emotional arousal (Cuthbert et al., 2000). Using *k*-means cluster analysis, which is a multivariate statistical technique designed to partition individual cases (participants) into *k*-groups such that variance is minimized within groups and maximized between groups (Hair and Black, 2000; Johnson and Wichern, 2002), we identified two distinct groups of smokers based on their LPPs to cigarette-related, pleasant, unpleasant, and neutral cues. One group (Group 1) was characterized by larger LPPs to pleasant stimuli than to cigarette-related cues. The other group (Group 2) was characterized by larger LPPs to cigarette-related cues than to pleasant stimuli. Importantly, smokers in Group 2, i.e., those with larger LPPs to cigarette cues than to pleasant stimuli, had a reduced likelihood of achieving long-term smoking abstinence over the course of a six-month smoking-cessation clinical trial (Versace et al., 2012). In another study (Versace et al., 2014), we used functional magnetic resonance imaging (fMRI) to identify specific brain regions where individual smokers differ in their brain responses to cigarette-related and pleasant stimuli. Again, we used cluster analysis to divide smokers into two groups and found that smokers in Group 1 showed larger brain responses to pleasant stimuli than to cigarette cues, and those in Group 2 showed the opposite pattern of brain responses. As was the case in the LPP study, the smokers in Group 2 in the fMRI study were also less likely to achieve long-term abstinence over the course of a six-month quit attempt. Importantly, the differences in brain activation in response to pleasant stimuli and cigarette cues were observed not only in the visual areas (the neural generators of the LPP; Keil et al., 2002; Liu et al., 2012; Sabatinelli et al., 2007), but also in the striatum, anterior cingulate cortex, and medial prefrontal cortex, all of which have been implicated in reward processing (Jasinska et al., 2014). These results support the hypothesis that, in some smokers (i.e., those in Group

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2), brain reward circuits are biased toward cigarette cues at the expense of other forms of reinforcement (Volkow et al., 2010).

It is unknown whether blunted brain responses to pleasant stimuli are a consequence of nicotine use (Volkow et al., 2010), or if they precede smoking initiation and increase the risk of nicotine dependence (Audrain-McGovern et al., 2012). Our previous studies were conducted in regular smokers who, on average, smoked 20 cigarettes per day for 25 years (Versace et al., 2014, 2012). Thus, the different brain reactivity profiles that we observed could have been pre-existing, or they could have emerged at some point after smoking initiation (e.g., at the transition from casual smoking to nicotine dependence). It is important to identify when smokers begin to show differences in brain responses to cigarette cues and pleasant stimuli because, in addition to predicting the likelihood of successfully quitting, it might also be possible to use this neural biomarker to predict other outcomes, such as smoking initiation or the transition from relatively early stages of cigarette use to nicotine dependence.

Ultimately, longitudinal studies will be necessary to determine whether differential brain responses to cigarette cues and pleasant stimuli predict smoking initiation or escalation. Prior to undertaking longitudinal research, it is prudent to determine whether a similar pattern of brain responses to those seen in heavy smokers attempting to quit can also be observed in younger, lighter smokers. Hence, to achieve this goal, we decided to apply the same cluster analytic method that we used in our studies of heavy smokers to a previously-unpublished LPP dataset collected as part of a larger study about emotional reactivity in smokers (Engelmann et al., 2011). Most of the smokers in this study were 18–25 years old, which is when smoking prevalence peaks (Substance Abuse and Health Services Administration, 2012) and patterns of cigarette use start to solidify (Hu et al., 2012). We partitioned smokers into $k = 2$ groups based on the amplitude of their LPPs to cigarette-related, pleasant, unpleasant, and neutral stimuli. We decided to use $k = 2$ groups because, based on our previous research, we expected to find individual differences in relative reactivity to cigarette-related and pleasant cues, i.e., one group with larger brain responses to cigarette cues than to pleasant stimuli, and another group with significantly larger brain responses to pleasant stimuli than to cigarette cues.

2. Materials and methods

2.1. Participants

Of 81 participants enrolled in the parent study, 45 daily smokers aged 18–25 with LPP data available were included in the cluster analysis. Participants not included in the cluster analysis consisted of 2 individuals who withdrew from the study, 5 for whom equipment failure resulted in a loss of data, 3 with excessive artifact in their EEG data, 20 non-smokers, and 6 smokers over the age of 25. Non-smokers were not included in the cluster analysis because the goal of this analysis was to determine whether young smokers show a pattern of individual differences in brain responses to pleasant and cigarette-related cues that was similar to what we previously observed in heavy smokers interested in quitting. Thus, we had no specific *a priori* hypotheses about how non-smokers would respond to cigarette cues, or about how their responses to cigarette cues would differ from pleasant stimuli. However, we did include the non-smokers ($n = 19$) in an exploratory analysis for which they were used as a reference group against which to compare the two groups of smokers (data from 1 non-smoker over the age of 25 were excluded).

Participants were recruited via advertisements seeking smokers not currently interested in quitting. Smokers were included if they reported smoking at least 1 cigarette per day for at least the past 30 days. Non-smokers were included if they reported not smoking a single cigarette over the past 6 months, and smoking no more than 100 cigarettes in their lifetime. Participants were excluded if they reported current uncontrolled psychiatric or medical illness, or the use of medications that might influence the ERP recording. All participants provided informed consent and all procedures were approved by the University of Minnesota's institutional review board. Participants received $50 or course credit for completing the study.

2.2. Procedure

The full procedure is described elsewhere (Engelmann et al., 2011). Briefly, participants attended three study visits: baseline, psychophysiological recording, and follow-up. During the baseline visit, smokers were randomly assigned to an abstinent or non-abstinent condition. At the time of psychophysiological recording, the abstinent smokers ($n = 23$) were 24 h into a 48 h abstinence period, whereas the non-abstinent smokers ($n = 22$) were instructed to smoke normally during the same period, and to smoke one additional cigarette at the start of the session (approximately 20 min elapsed between when this cigarette was smoked and the start of data collection).

During the baseline visit, nicotine dependence was assessed using the Fagerström Test of Nicotine Dependence (FTND; Heatherton et al., 1991) and Heaviness of Smoking Index (HSI; Heatherton et al., 1989). At the start of all visits, the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami, 1998) and Factor 1 of the Questionnaire of Smoking Urges (QSU; Tiffany and Drobes, 1991) were used to assess nicotine withdrawal symptoms and cigarette craving. Due to a recording error, FTND, HSI, MNWS, and QSU data were lost from 1 participant assigned to the non-abstinent condition.

Participants viewed a series of 60 pictures, 15 from each of four categories: cigarette, pleasant, unpleasant, and neutral. Pictures were presented for 6 s each in a random order, separated by an intertrial interval lasting 18–24 s (Cuthbert et al., 2000). Pictures were selected from the International Affective Picture System (IAPS; Lang et al., 2005) and from picture sets developed by the authors (Carter et al., 2006; Engelmann et al., 2011). The electroencephalogram (EEG) was recorded from electrodes placed at the Fz, Cz, and Pz sites of the International 10–20 system (Jasper, 1958), referenced to linked mastoids. Vertical electrooculogram (vEOG) was measured for the purpose of correcting eye-movement artifacts in the EEG. Using established procedures for measuring the LPP (Cuthbert et al., 2000; Sabatinelli et al., 2007; Schupp et al., 2000; Versace et al., 2011), the EEG and vEOG were bandpass filtered (0.1–40 Hz), amplified, and continuously sampled at a rate of 125 Hz using a PC running VPM software (Cook, 2003).

2.3. Statistical analysis

We analyzed data from the Cz electrode site, which is where the LPP is most reliably observed (Cuthbert et al., 2000; Keil et al., 2002; Schupp et al., 2000) and where the LPP was localized in our previous study of individual differences in LPP magnitude in smokers (Versace et al., 2012). EEG data were processed using established procedures, which included digital filtering (0.1–30 Hz), epoch extraction (120 ms before through 1000 ms after picture onset), artifact detection and rejection, averaging across trials within each participant and picture category to compute the ERP, eye-movement correction (Gratton et al., 1983), and baseline correction. In cases where there were fewer than 10 artifact-free trials in any stimulus category for a particular participant, the data for that participant were excluded from further analysis ($n = 3$). Aver-