Archival Report

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Brain Responses to Smoking Cues Differ Based on Nicotine Metabolism Rate

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ABSTRACT

BACKGROUND: Inherited differences in the rate of metabolism of nicotine, the addictive chemical in tobacco, affect smoking behavior and quitting success. The nicotine metabolite ratio (3′-hydroxycotinine/cotinine) is a reliable measure of nicotine clearance and a well-validated predictive biomarker of response to pharmacotherapy. To clarify the mechanisms underlying these associations, we investigated the neural responses to smoking cues in normal and slow nicotine metabolizers.

METHODS: Treatment-seeking smokers ($N = 69$; 30 slow metabolizers and 39 normal metabolizers) completed a visual cue reactivity task during functional magnetic resonance imaging on two separate occasions: once during smoking satiety and once after 24 hours of smoking abstinence.

RESULTS: In whole-brain analysis, normal (compared with slow) metabolizers exhibited heightened abstinence-induced neural responses to smoking cues in the left caudate, left inferior frontal gyrus, and left frontal pole. These effects were more pronounced when extreme groups of slow and normal metabolizers were examined. Greater activation in the left caudate and left frontal pole was associated with abstinence-induced subjective cravings to smoke.

CONCLUSIONS: Inherited differences in rate of nicotine elimination may drive neural responses to smoking cues during early abstinence, providing a plausible mechanism to explain differences in smoking behaviors and response to cessation treatment. Normal metabolizers may benefit from adjunctive behavioral smoking cessation treatments, such as cue exposure therapy.

Keywords: Cue reactivity, Neuroimaging, Nicotine, Nicotine addiction, Nicotine metabolite ratio, Withdrawal

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Tobacco dependence is a chronic relapsing disorder affecting approximately one in five adults in the United States, with considerable health consequences (1,2). Inherited differences in the rates of metabolism and resulting clearance of nicotine, the addictive chemical in tobacco, affect smoking behavior and quitting success; slower metabolizers tend to smoke less and have higher quit rates than normal metabolizers (3–6). Nicotine is primarily metabolized by the liver enzyme CYP2A6 to cotinine, which itself is metabolized to 3′-hydroxycotinine by the same enzyme. The ratio of 3′-hydroxycotinine to cotinine provides a stable and reliable measure of individual differences in nicotine metabolism rate, referred to as the nicotine metabolite ratio (NMR) (7–10). Building on prior trials (6,11,12), a large multisite, placebo-controlled, randomized clinical trial validated the NMR as a predictive biomarker of the relative efficacy of two widely used smoking cessation medications: the transdermal nicotine patch and varenicline (13).

Despite the well-documented differences between slow metabolizers and normal metabolizers in response to smoking cessation treatment, the mechanisms underlying these effects are not well understood. Slow metabolizers have been shown to smoke fewer cigarettes per day than normal metabolizers; however, these effects tend to be modest (3,4). Associations between the NMR and nicotine dependence, withdrawal symptoms, and craving during cessation are inconsistent (12,14–16). It is possible that differences between slow metabolizers and normal metabolizers in smoking cessation are mediated by alterations in nicotinic receptor availability. Normal metabolizers show greater nicotinic receptor availability during early abstinence, an effect that may result from faster clearance of nicotine from the brain, greater receptor upregulation during chronic exposure, or a combination of the two (17). Differences in fluctuation of nicotine levels and nicotinic receptor availability throughout the day could also increase the rewarding effects of nicotine in normal metabolizers compared with slow metabolizers (18). A neuroimaging study found that compared with slow metabolizers, normal metabolizers exhibit greater neural responses to conditioned smoking cues in brain regions within dopamine-dependent reward circuitry, suggesting a plausible mechanism to explain their lower quit rates (19). However, in this prior study, neuroimaging was performed at a single time point when participants were smoking as usual. Because slow metabolizers and normal metabolizers may clear nicotine from the brain at

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different rates (17), evaluating smoking cue–elicited brain responses during both abstinence and smoking satiety is necessary to clarify the neurobehavioral mechanisms that may underlie differences in quitting success and therapeutic response.

We completed a within-subject crossover functional magnetic resonance imaging (fMRI) study to examine brain responses to visual smoking cues (vs. neutral images) in slow metabolizers and normal metabolizers during two sessions: 24-hour abstinence challenge versus smoking satiety. Because of more rapid nicotine elimination in normal metabolizers compared with slow metabolizers, we hypothesized that normal metabolizers would exhibit heightened cue responses in the mesocorticolimbic circuitry during the abstinent condition compared with the smoking condition. Given the clinical relevance of neural responses to smoking cues for quitting success (20), these data could inform the design of targeted therapies for smokers with variable nicotine metabolism.

METHODS AND MATERIALS

Participants

Participants were treatment-seeking smokers 18–65 years old who reported smoking ≥10 cigarettes per day (CPD) for ≥6 months and were recruited through media advertisements. Exclusion criteria were current use of nicotine products other than cigarettes (e.g., chewing tobacco, snuff, e-cigarettes, or smoking cessation products); pregnancy, planned pregnancy, or breastfeeding; history of DSM-IV Axis I psychiatric or substance disorders except nicotine dependence (assessed by the Mini-International Neuropsychiatric Interview) (21); use of psychotropic medications; history of brain injury; left-handedness; material in the body contraindicating fMRI; low or borderline intelligence (<90 score on Shipley's IQ test) (22); and any impairment that would prevent task performance.

Procedures

Screening. All procedures were approved by the University of Pennsylvania Institutional Review Board and carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent and completed a urine drug screen and breath alcohol test; women completed a urine pregnancy test. Eligible participants completed the Fagerström Test for Nicotine Dependence (FTND) (23) and provided a saliva sample for NMR determination (7,8).

NMR Determination. Concentrations of cotinine and 3′-hydroxycotinine in saliva samples taken during baseline smoking were determined by liquid chromatography–tandem mass spectrometry, and the NMR was calculated for each participant (7). Clinical trial data demonstrated differences in quit rates and medication response between slow metabolizers and normal metabolizers using a plasma NMR cut point of ≤.31 for inclusion as slow metabolizers (13). Plasma NMR and saliva NMR are highly correlated; based on previously published regression coefficients (8), a .31 plasma cut-point corresponds to a saliva cut-point of .22. To verify this, we obtained plasma NMR values from a subset (n = 32) of participants and used regression modeling to calculate a value for saliva NMR equivalent to a plasma NMR of .31 in this sample. Our modeling indicated a value of .21 in saliva, which is similar to the value obtained using the published model. Based on this regression model, we divided participants into slow metabolizers (saliva NMR ≤ .21) and normal metabolizers (saliva NMR > .21).

Scan Day Procedures. The neuroimaging experiment used a within-subject design with two blood oxygen level–dependent (BOLD) fMRI sessions scheduled 1–3 weeks apart in counterbalanced order: 1) smoking satiety and 2) 24-hour abstinence. Subjects were instructed to refrain from alcohol or other drugs for at least 24 hours before the session. Subjects with a positive drug screen, a breath alcohol test >.01, or a breath carbon monoxide test >9 ppm (abstinent session only) were excluded. For the smoking condition, participants smoked a single cigarette about 1 hour before cue exposure.

Image Acquisition

The BOLD fMRI was acquired with a MAGNETOM Trio 3-Tesla system (Siemens, Erlangen, Germany) using a whole-brain, single-shot gradient-echo echo planar sequence with the following parameters: repetition time/echo time = 3000/30 ms, field of view = 220 mm, matrix = 64 × 64, slice thickness/gap = 3.4/0 mm, 48 slices, effective voxel resolution of 3.4 × 3.4 × 3.4 mm. Radiofrequency transmission used a quadrature body coil and reception used a 32-channel head coil. Before BOLD fMRI, 5-minute magnetization prepared rapid acquisition gradient-echo T1-weighted imaging (repetition time 1620 ms, echo time 3.87 ms, field of view 50 mm, matrix 192 × 256, effective voxel resolution of 1 × 1 × 1 mm) was acquired for anatomic overlays of functional data and to aid spatial normalization to standard atlas space.

Cue Reactivity Task

The cue reactivity task consisted of exposure to color pictures of smoking-related and neutral images in a pseudorandom, event-related design. Smoking-related images were pictures of people smoking or smoking-related objects, such as cigarettes or ashtrays. Neutral images (control condition) were pictures of people engaged in everyday tasks or unrelated objects, such as pencils. Neutral and smoking images were matched for visual features such as size, shape, and luminosity; images of people were balanced for gender. Each image was presented for 500 ms followed by a blank screen with a fixation point; the interstimulus interval was 1.5–13.5 seconds (mean 3.47 seconds). The total task time was ~8 minutes. A two-item subjective craving questionnaire was administered at three time points during the scan: immediately after structural and resting scans (~15 minutes into BOLD scanning), immediately before the cue task (~50 minutes into BOLD scanning) and immediately after the cue task (24). During the time between the structural and resting scans and the cue task, participants were scanned while completing tasks assessing cognitive function, including working memory, attention, and response inhibition; data from these tasks were reported elsewhere (25,26). Participants were asked to rate the degree

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