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Individual differences in amygdala reactivity following nicotinic receptor stimulation in abstinent smokers

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ABSTRACT

Hyperactive amygdala functioning may underlie emotional dysregulation during smoking abstinence and represents one neurobiological target for pharmacological cessation aids. Available pharmacotherapies (e.g., nicotine replacement and varenicline) aid only a subset of individuals with smoking cessation and therefore elucidating the neurobiological impact of these medications is critical to expedite improved interventions. In a fMRI study employing a within-subject, double-blind, placebo-controlled design, we assessed task performance and amygdala functioning during an emotional face matching paradigm following administration of nicotine and varenicline to 24 abstinent smokers and 20 nonsmokers. All participants underwent ~17 days of varenicline and placebo pill administration and were scanned, on different days under each condition, wearing a transdermal nicotine or placebo patch. During the amygdala reactivity paradigm, nicotinic acetylcholine receptor (nAChR) stimulation by nicotine and varenicline decreased reaction time (RT) in abstinent smokers but not in nonsmokers. When considering all smokers as a single homogenous group, no drug-induced effects on amygdala reactivity were detected. However, in an exploratory analysis we parsed participants into subgroups according to individual differences in the propensity to demonstrate stable performance augmentation following nAChR stimulation (stable RT-improvers [SI] vs. variable RT-improvers [VI]). Using this exploratory approach, drugs appeared to modulate amygdala reactivity in only one smoker subgroup but not in either nonsmoker subgroup. Specifically, in the SI-smoker cohort abstinence-induced elevated amygdala reactivity was down-regulated by nAChR stimulation. In contrast, varenicline and nicotine did not modulate amygdala functioning in the VI-smoker cohort who displayed moderate levels of amygdala reactivity in the absence of drug administration. These results suggest that pharmacotherapies most robustly dampened amygdala functioning in smokers appearing susceptible to abstinence-induced effects. Such findings provide a step towards fractionating the smoker phenotype by discrete neurobiological characteristics.
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Introduction

A major impediment for cigarette smokers attempting to quit is the tobacco abstinence syndrome characterized by anxiety, irritability, and difficulty concentrating (Hughes, 2007; Piasecki, 2006). Nicotine reverses abstinence-induced emotional dysregulation (Kassel et al., 2003) and performance deficits (Heishman et al., 1994) suggesting that early relapse occurs, in part, to relieve such symptoms (Baker et al., 2004). Indeed, those smokers presenting with higher degrees of affective disturbances and/or poorer task performance shortly after cessation are those most liable for recidivism (Patterson et al., 2010; Piper et al., 2011). Thus, early abstinence represents a critical period for interventions to assist smokers with cessation. Currently available pharmacological cessation aids (e.g., varenicline and nicotine replacement) are efficacious in only a subset of individuals and therefore elucidation of the neurobiological impact of these medications is important to expedite the development of improved interventions.

Amygdala's role in affect-related processes is well established (Phelps and LeDoux, 2005) and the neural substrates mediating negative emotional states during acute drug abstinence are critically centered on amygdala and its interconnected circuitry (Koob, 2009; Koob and Le Moal, 2005). In chronic smokers acutely deprived of nicotine, elevated amygdala activity co-varies with increased smoking urges (Wang et al., 2007) and cigarette smoking dampens this regional hyperactivity (Rose et al., 2003; Zubieta et al., 2005). Additionally, elevated amygdalar responses to smoking-related cues have been associated with increased smoking urges (Chase et al., 2011; Kuhn and Gallinat, 2011; Smolka et al., 2006) and greater susceptibility to relapse (Janes et al., 2010). Such findings suggest that

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amelioration of hyperactive amygdala functioning represents one neurobiological target upon which cessation pharmacotherapies may exert an efficacious response, particularly in the subset of smokers with greater abstinence-induced hyperactivity. Recent neuroimaging investigations indicate that varenicline, the first non-nicotine medication specifically developed for smoking cessation, down-regulates amygdala functioning in chronic smokers (Franklin et al., 2011a; Loughead et al., 2010, 2011).

Varenicline is thought to aid cessation by ameliorating aversive withdrawal symptoms during abstinence while *also* attenuating nicotine's reinforcing effects upon re-exposure. In nicotine's absence, varenicline acts primarily as a partial agonist at $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs) producing ~50–60% the relative action of nicotine; whereas in nicotine's presence, the drug acts as an antagonist, binding with higher affinity and preventing full activation by nicotine (Rollema et al., 2007). Varenicline-induced effects in animal models of mood and cognition appear mediated by $\alpha_4\beta_2$ and/or α_7 nAChR interactions (Rollema et al., 2009). In the clinic, varenicline reduces abstinence-induced affective and cognitive disturbances as well as the subjective rewarding aspects of a smoked cigarette (Patterson et al., 2009). This partial agonist/antagonist profile, targeting both negative and positive reinforcement mechanisms perpetuating tobacco use, may account for varenicline's greater relative efficacy over other pharmacotherapies (Gonzales et al., 2006; Jorenby et al., 2006). We modeled this putative "dual action" profile by administering varenicline alone *and* in combination with transdermal nicotine to a group of overnight abstinent smokers, as well as to a nonsmoker (negative control) group.

The primary aim of this study was to use the partial agonist/antagonist varenicline and the full agonist nicotine as pharmacological probes to interrogate abstinence-induced effects on amygdala functioning and to assess potential differential pharmacological responses in subsets of smokers. To examine amygdala functioning, we employed functional magnetic resonance imaging (fMRI) coupled with an emotional face matching paradigm known to yield a reliable measure of amygdala reactivity (Hariri et al., 2002b; Sergerie et al., 2008) and previously utilized to assess the impact of pharmacological manipulations (Bigos et al., 2008; Labuschagne et al., 2010; Paulus et al., 2005). In a placebo-controlled, within-subject design, participants underwent ~17 days each of varenicline and placebo pill administration (PILL factor) and were scanned near the end of both medication periods wearing, on different days, a transdermal nicotine or placebo patch (PATCH factor). Based on preclinical data regarding the pharmacological properties of varenicline (Rollema et al., 2009) and operationalized in the current study, we anticipated varenicline (PILL) × nicotine (PATCH) interactions across dependent variables (Fig. 1A). We hypothesized: 1) varenicline and nicotine would speed reaction times (RT) in abstinent smokers but not in nonsmokers; and 2) these pharmacological probes would dampen abstinence-induced elevated amygdala reactivity in smokers. We further examined differential amygdalar responses following drug administration in an *exploratory* analysis by parsing individuals into "stable" versus "variable/non RT-improvers" according to the degree to which nAChR stimulation augmented task performance. Using a decrease in RT following drug administration (relative to a corresponding placebo) as a proxy for a drug response, we operationally defined stable RT-improvers (SI) as those participants showing RT decreases following *all* drug administrations, whereas variable/non RT-improvers were defined as those who did not show a RT decrease following all drug administrations. We reasoned that those smokers demonstrating stable RT-improvements following nAChR stimulation would also be those most likely to show drug-induced changes in regional brain functioning.

Material and methods

Participants

A total of 24 cigarette smokers (12 females) and 20 nonsmokers (10 females), all right-handed and 18–55 years of age completed the study. Participants reported no history of drug dependence (other than nicotine in smokers), neurological or psychiatric disorders, cardiovascular or renal impairment, diabetes, or contra-indications for MRI scanning. We recruited non-treatment seeking daily smokers who reported smoking 10 or more cigarettes per day for a minimum of 2 years. Nonsmokers reported no history of daily cigarette use and no smoking within 2 years preceding the study. Participant characteristics are reported in Table 1. Notably, the smoker sample was older ($p = 0.04$) and less educated than the nonsmoker sample ($p = 0.004$). As such, age and years of education were included as covariates when comparing smokers versus nonsmokers. Data from two male nonsmokers were excluded from behavioral and imaging analyses due to excessive head motion during scanning. Before beginning the study, participants gave written informed consent in accordance with the Institutional Review Board for the National Institute on Drug Abuse

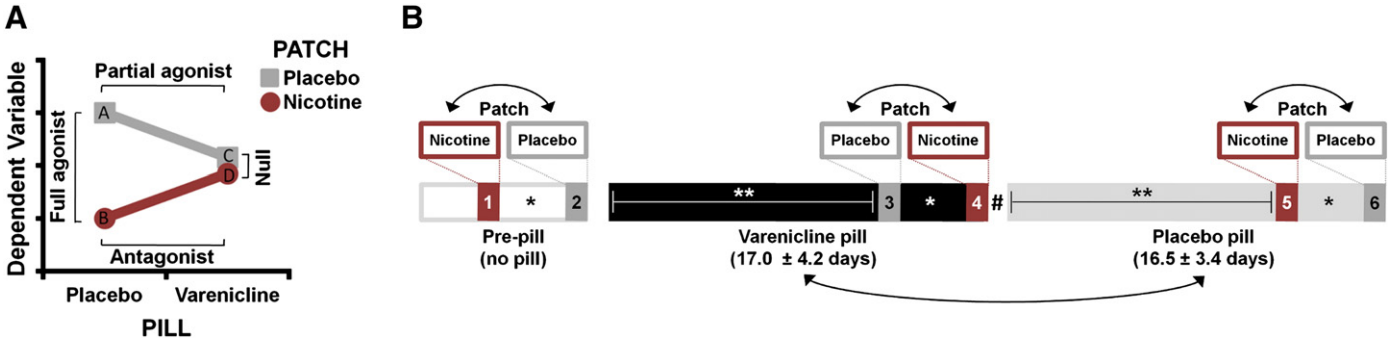

Fig. 1. Study overview schematics. (A) Illustration of anticipated varenicline (PILL) × nicotine (PATCH) pharmacological interaction and the nature of effects on a dependent variable (DV) during smoking abstinence. Abstinence-induced effects on the DV (e.g., reaction time, amygdala reactivity) are expected to be greatest following smoking deprivation and in the absence of drug administration (i.e., under placebo-pill/placebo-patch conditions: data point "A"). Administration of nicotine is expected to reduce this abstinence-induced elevation (data point "B") yielding a full agonist response (A vs. B). Similarly, administration of varenicline alone is expected to reduce the DV (data point "C") yielding a partial agonist effect (A vs. C). Administration of varenicline in combination with nicotine (data point "D") is then expected to attenuate the nicotine-induced response, as varenicline binds to nAChRs with higher affinity than nicotine and blocks the full agonist response, yielding an antagonist effect (B vs. D). These partial agonist and antagonist effects combine to produce a null effect of nicotine versus placebo patch (C vs. D) in the presence of varenicline. (B) Illustration of study design. All participants completed six fMRI assessments. Before beginning a pill regimen (pre-pill), participants completed assessments wearing transdermal nicotine and placebo patches on separate days. Subsequently, participants underwent varenicline (mean ± SD: 17.0 ± 4.2 days) and placebo pill administration (16.5 ± 3.4 days) and again completed nicotine and placebo patch scans towards the end of both medication periods. Double-headed arrows indicate the randomization of drug order across participants. * Nicotine and placebo patch scans were separated by an average of 2.9 ± 1.7 days. ** Neuroimaging assessments occurred 13.9 ± 2.3 days after the onset of each PILL period. # A washout interval did not separate varenicline and placebo pill epochs.