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Brain substrates of early (4 h) cigarette abstinence: Identification of treatment targets

Teresa R. Franklin[a,*], Kanchana Jagannathan[a], Nathan Hager[a], Zhuo Fang[a,b,c], Sihua Xu[b,c], Joyce Wong[a], Anna Rose Childress[a], John A. Detre[b], Hengyi Rao[a,b,c], Reagan Wetherill[a]

[a] Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, 19104, USA
[b] Department of Neurology, University of Pennsylvania, Philadelphia, PA, 19104, USA
[c] Laboratory of Applied Brain and Cognitive Sciences, Shanghai International Studies University, Shanghai, China

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ABSTRACT

Introduction: Research indicates that overnight nicotine abstinence disrupts neural activity in the mesocorticolimbic reward network; however, less is known about the time course of abstinence-induced brain changes. To examine the potential neural effects of early abstinence, we used arterial spin labeling perfusion fMRI, to measure regional cerebral blood flow (rCBF) changes in the resting brain induced by 4 h of nicotine abstinence.
Methods: In a repeated measures design, 5 min of resting perfusion fMRI data were acquired in awake nicotine-dependent individuals (eyes open) during 'smoking as usual' (SMK) and following 4 h of monitored nicotine abstinence (ABS) conditions (N = 20). Conditions were compared using a paired *t* test in SPM8. Craving was assessed prior to each condition.
Results: Compared to SMK, ABS significantly increased craving and reduced rCBF in select regions, including the hippocampus and ventral striatum (cluster corr, $\alpha = 0.01$, 943 contiguous voxels). The magnitude of the abstinence-induced change in rCBF correlated with the magnitude of the change in craving across conditions in select regions, including the medial and lateral orbitofrontal cortices and the anterior ventral insula (r values ranging from 0.59–0.74).
Conclusions: Results show that as few as 4 h of abstinence can reduce resting rCBF in multiple nodes of the brain's mesocorticolimbic network, disrupting neural processing. Identifying early withdrawal treatment targets has far-reaching implications, which include thwarting relapse proclivities. Results parallel those of the extant human literature and are in agreement with an extensive preclinical literature showing compromised mesolimbic dopaminergic function and impairments in reward function during nicotine withdrawal.

1. Introduction

Cigarette smoking is the leading cause of preventable disease and premature death, yet one in five adults in the United States continue to smoke (World Health Organization, 2015). Many of these individuals have a strong desire to quit smoking; however, their quit attempts are often unsuccessful, and relapse after a short cessation period is typical (Baillie et al., 1995; Hughes et al., 2008). A host of factors may be involved in the motivation to smoke and the risk of relapse, including exposure to smoking reminders (cues), stress, peer pressure, availability, hormonal status and weight management (Baker et al., 1986; Caggiula et al., 2001; Dagher et al., 2009; Franklin et al., 2008; Janes et al., 2010; Killen and Fortmann, 1997; Perkins, 2001; Perkins et al., 2001; Rose, 1996; Sinha and Li, 2007). Of note, withdrawal-induced craving is cited as a major motivator for continued smoking and relapse, particularly in the early phases of smoking cessation (Baker et al., 2004; Doherty et al., 1995; Piper et al., 2011). Withdrawal is an intense phase of smoking cessation, roused by the absence of the pharmacological effects of nicotine on its brain targets (Rada et al., 2001). Nicotine's terminal half-life is approximately two hours; thus, conservative estimates might place the onset of withdrawal within two hours after last smoking (Benowitz et al., 1982); however, withdrawal symptoms can emerge as early as 30 min after smoking (Hendricks et al., 2006). Withdrawal is characterized by a constellation of symptoms including anger, irritability and restlessness, anxiety, dysphoria, difficulty with focus and attention, and sleep problems including insomnia (Hatsukami et al., 1985; Hendricks et al., 2006; Hughes, 2007). Generally, to our knowledge, symptoms are the most severe within the

* Corresponding author at: Center for the Studies of Addiction, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, Philadelphia, PA 19104, USA.
E-mail address: teresafr@pennmedicine.upenn.edu (T.R. Franklin).

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first 24–72 h and continue for 2–4 weeks (Hendricks et al., 2006; Hughes, 2007). Notably, most individuals who attempt to abstain from smoking lapse within the first several hours after quitting, prompting Hendricks et al. (2006) to conduct a comprehensive multi-modal assessment of early withdrawal to provide a scientific basis for the observed phenomenon. As little as 1 h of monitored abstinence produced deficits in sustained attention, and reductions in heart rate and increased self-reported withdrawal symptoms (*i.e.*, anger, anxiety, craving) that dramatically intensified over the course of 4 h (Hendricks et al., 2006).

The neural mechanisms underlying the abstinence-induced syndrome and how smoking relieves such symptoms are only partially understood. As suggested by the available literature and the sensitization-homeostasis theory of drug addiction (Robinson and Berridge, 2008) nicotine's indirect effects on the dopaminergic system may underlie the motivation to seek and use nicotine. When nicotine is present in the brain, it enhances dopamine release in the ventral striatum and attenuates motivation to seek drug (Corrigall et al., 1992; Di Chiara and Imperato, 1988; Natividad et al., 2010; Rada et al., 2001). In contrast, when nicotine levels decline, as during abstinence, striatal dopamine levels decrease and motivation to seek and use drugs is enhanced (Corrigall et al., 1992; Di Chiara and Imperato, 1988; Epping-Jordan et al., 1998; Natividad et al., 2010; Rada et al., 2001; Zhang et al., 2012). Although not always the case, some studies have shown that mesolimbic activation correlates with dopamine release in humans (Schott et al., 2008), suggesting that activation of the mesolimbic pathway may be considered a surrogate marker of dopaminergic activity. In line with the preclinical data, in human work, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies show that cigarette smoking and/or nicotine administration increases resting brain response in striatal areas and other regions of the mesolimbic system, including the amygdala, anterior cingulate cortex, frontal lobe, and thalamus (Domino et al., 2013; Stein et al., 1998; Tanabe et al., 2008; Zubieta et al., 2005).

Despite the physiological (Cruickshank et al., 1989; Domino et al., 2013; Hendricks et al., 2006) and behavioral (Hendricks et al., 2006) evidence for early withdrawal, all of the neuroimaging studies examining the effects of nicotine abstinence on regional resting brain response have been conducted in overnight abstinent smokers (Domino et al., 2013; Stein et al., 1998; Tanabe et al., 2008; Zubieta et al., 2005); however, studies examining other brain end points at earlier time points have been conducted. Hong et al. (2009) examined resting-state cingulate functional connectivity in individuals who had abstained from smoking for 4.5 h and then were administered either nicotine or placebo patch to determine the effects of acute nicotine administration on cingulate connectivity. Acute nicotine was found to enhance cingulate-neocortical functional connectivity patterns (Hong et al., 2009). Brain responses during a monetary incentive reward task have also been shown to differ in participants 2.5 h after smoking (a period chosen to minimize early withdrawal effects) when imaged under placebo versus nicotine patch conditions, with acute nicotine increasing activity in the dorsal striatum for anticipated magnitude of reward (Rose et al., 2013). Neither of these studies examined rCBF. Given the available data, we hypothesized that shorter periods of abstinence may also alter resting rCBF. Specifically, we hypothesized that 4 h of nicotine deprivation versus 'smoking as usual' would disrupt resting rCBF in key nodes within mesocorticolimbic circuitry.

Testing the hypothesis that 4 h of abstinence can perturb the brain is important for at least two reasons. Primarily, it will characterize the functional substrates of early withdrawal, which has not been shown previously and which may have meaningful implications for the treatment of cigarette dependence. Given that most lapses occur within hours after attempting to abstain and are motivated by the absence of nicotine in the brain, which promotes the abstinence syndrome, knowledge of the brain substrates of early withdrawal would offer a rational target for medications development. This knowledge would also be useful for the development of short-term relief medications for smokers who are not quite ready to make a quit attempt and yet who may be forbidden to smoke in the work place and in most hotels, airports, etc. For example, in the U.S., smoking is banned in most internal work environments and given that even 1 h of abstinence produced deficits in sustained attention, reductions in heart rate, and increased self-reported withdrawal symptoms (Hendricks et al., 2006), current moderate to heavy smokers are likely experiencing withdrawal symptoms during work hours, reducing their ability to attend, focus and respond appropriately to stress. Identifying the brain substrates of early abstinence is a first step in the development of effective treatments that may relieve withdrawal symptoms throughout the day, which may improve work productivity and aid smokers in their goal of quitting. Secondarily, on a practical level, if effects of abstinence can be observed in compressed time frames, many of the caveats associated with the measurement of overnight abstinence for research purposes can be minimized. For example, unequivocal overnight smoking abstinence cannot be established in an outpatient laboratory experiment. The current methods used to gauge overnight abstinence are through carbon monoxide (CO) measurements from exhaled breath or self-report. Both methods are unreliable as CO levels rapidly decrease after smoking and can fall below 10 ppm in as little as 3 h (Hendricks et al., 2006) and treatment-seeking smokers are known to misrepresent their smoking status (Gariti et al., 2002). Another caveat introduced by relying on CO levels in experimental research is a lack of standardization of time since last smoked, which could be as little as 3 h or as great as 18 h prior to obtaining a CO measurement. Failure to standardize time since last smoked can introduce noise, resulting in inaccurate reporting. Therefore, restricting the window for studying the effects of withdrawal on brain and behavioral endpoints to occur within the time constraints of a laboratory session would reduce costs and improve scientific rigor.

To test the hypothesis that brief periods of abstinence may affect brain blood flow selectively in mesocorticolimbic circuits, we used arterial spin labeling (ASL) perfusion fMRI to measure absolute resting rCBF in smokers when smoking as usual and following 4 h of monitored abstinence. Perfusion refers to the delivery of oxygen and nutrients to tissue by means of blood flow and is regionally coupled to brain metabolism and, therefore, neural activity (Aguirre et al., 2005). Similar to PET, perfusion fMRI is quantitative (ml of blood/100 g of tissue/minute) (Aguirre et al., 2005; Franklin et al., 2011a), and is therefore preferable for longitudinal studies examining the effects of state versus the more widely used blood oxygen level dependent (BOLD) fMRI technique. We have successfully used the quantitative perfusion fMRI technique over the last 10 years to elucidate the brain substrates of smoking cue reactivity, the effects of medications on resting brain blood flow and to identify individual differences in smoking cue reactivity and resting brain blood flow (Franklin et al., 2011a,b; Franklin et al., 2015a,b; Franklin et al., 2012; Franklin et al., 2007; Wetherill et al., 2014; Wetherill et al., 2013).

2. Methods

2.1. Participants

The study was conducted at the University of Pennsylvania Perelman School of Medicine. All procedures were approved and monitored by the Institutional Review Board, and adhered to the Declaration of Helsinki. Participants received compensation ranging from $235 to $250 for participating in the study. Eligible participants were non-treatment-seeking smokers (18–60 years of age) who reported smoking at least 10 cigarettes per day for the past 3 years and had baseline carbon monoxide (CO) levels greater than 10 ppm. Ten CPD was chosen as the smoking criteria to study the effects of 4 h of abstinence because 1) 10 CPD represents the average smoker in the current climate, wherein smoking is largely prohibited in the work place and most other public places in the U.S; 2) a 10 CPD individual scores in