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Prefrontal hemodynamic changes during cigarette smoking in young adult smokers with and without ADHD☆

Jean-G. Gehricke [a,*], Chiara Polzonetti [a,b], Cyrus Caburian [a], Enrico Gratton [b]

[a] University of California Irvine, Department of Pediatrics, Irvine, CA, USA
[b] University of California Irvine, Department of Biomedical Engineering, Irvine, CA, USA

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ABSTRACT

Individuals with attention-deficit/hyperactivity disorder (ADHD) have elevated smoking prevalence and reduced cessation rates compared to the general population. However, the effects of cigarette smoking on underlying brain activity in smokers with ADHD are not well characterized. Non-invasive near-infrared spectroscopy (NIRS) was used to characterize how cigarette smoking affects prefrontal brain hemodynamics in smokers with and without ADHD. Prefrontal changes of oxy- and deoxyhemoglobin (HbO_2 and HHb) were measured in six male adult smokers with ADHD and six age- and gender-matched control smokers. NIRS measurements were separated into four sequential time intervals, i.e., before smoking, during smoking, after smoking, and during a breath hold. Prefrontal HbO_2 was lower during smoking in smokers with ADHD compared to control smokers. More specifically, smokers with ADHD showed decreased prefrontal HbO_2 during smoking compared to breath hold, before and after smoking periods. In contrast, control smokers showed increased prefrontal HbO_2 from before smoking to breath hold. Decreased prefrontal HbO_2 in smokers with ADHD may reflect a smoking-induced change in prefrontal brain activity and microvasculature, which is not found in smokers without ADHD. The lower prefrontal HbO_2 may be a biomarker for increased susceptibility to tobacco smoke in smokers with ADHD. Smoking in individuals with ADHD may increase vasoconstriction of cerebral arteries in the prefrontal cortex, which may contribute to a reduction in HbO_2. The findings highlight the importance of smoking cessation, in particular in those smokers who use nicotine to self-medicate ADHD symptoms.

1. Introduction

Cigarette smoking continues to be a major public health problem. The Centers for Disease Control and Prevention (CDC, 2009) estimated that cigarette smoking costs $193 billion per year in direct medical expenditures and costs associated with loss of productivity. Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, impulsivity and hyperactivity (APA, 2000) and has been identified as a risk factor for smoking initiation and subsequent nicotine addiction (Gehricke et al., 2009, 2007; Kollins et al., 2005; Milberger et al., 1997). The smoking prevalence rates among young adults with this disorder have been at about 40% for the last 15 years (McClave et al., 2010; Molina and Pelham, 2001; Pomerleau et al., 1995) compared to 22% in the general population (CDC, 2011). In addition, smokers with ADHD are less successful in smoking cessation (Covey et al., 2008; Pomerleau et al., 1995).

The high prevalence and low cessation rates may be the result of individuals with ADHD self-medicating with nicotine (Wilens et al., 2007). As suggested previously (Gehricke et al., 2007), the elevated risk of dependence and the greater difficulty in quitting in individuals with ADHD may result, in part, from nicotine's effects on prefrontal cortical brain areas. Prefrontal cortex (PFC) areas are rich in nicotinic acetylcholine receptors (nAChRs) (Ghatan et al., 1998) and play a major role in the pathophysiology of ADHD (Arnsten, 2009). Research has shown that cigarette cravings during abstinence activate the PFC (Brody et al., 2007; Zubieta et al., 2005), whereas varenicline (a partial agonist at alpha4beta2-nAChRs and antagonist at alpha7 nAChRs) reduces the activity in some of these regions (Franklin et al., 2011). Similarly, acute cigarette smoking has been shown to reduce brain regional cerebral blood flow (rCBF) and brain hemodynamic reactivity (Ghatan et al., 1998; Terborg et al., 2002), vascular reactivity, and oxygen consumption (Siafaka et al., 2007).

Given the elevated smoking prevalence rates and lower cessation rates, smokers with ADHD may show altered prefrontal hemodynamic characteristics in response to cigarette smoking. The primary aim of the study was to measure the acute prefrontal hemodynamic changes

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* Corresponding author at: University of California Irvine, Department of Pediatrics, School of Medicine, 1915 W. Orangewood Ave., Ste. 200, Irvine, CA 92612, USA. Tel.: +1 714 937 3647 (office).
E-mail address: jgehrick@uci.edu (J.-G. Gehricke).

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using near-infrared spectroscopy (NIRS) method during smoking in smokers with and without ADHD. NIRS uses principles of optical spectroscopy to detect brain hemodynamic changes such as changes in oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb) (Gratton et al., 1997, 2005). A secondary aim of the study was to measure prefrontal hemodynamic changes after smoking in response to oxygen deprivation (i.e., a breath hold), which indicates cerebral vasomotor reactivity (VMR). VMR is age-dependent (Safonova et al., 2004) and a result of baroreceptors reacting to increased pressure of carbon dioxide, which induces vasodilatation in the resistance levels, increasing blood flow velocity in the cerebral arteries and reducing the resistance of vessels (Molinari et al., 2006). Cerebral blood flow is mediated by dopamine (Choi et al., 2006), which is depressed in individuals with ADHD (Volkow et al., 2007). Based on the prefrontal and dopaminergic dysfunctions associated with ADHD, we hypothesized that smokers with ADHD show altered PFC hemodynamic characteristics compared to control smokers.

2. Materials and methods

2.1. Participants

Twelve young adult male smokers (6 ADHD and 6 controls) were recruited as part of a larger study on the effects of smoking on brain circuitry. Similar to previous studies (Gehricke et al., 2009, 2011), each participant was assessed according to DSM-IV-TR criteria (APA, 2000) with the structured clinical interview for DSM-IV (SCID; First et al., 1996), and the QUEST method (Wigal et al., 2007). Participants were excluded if they were treated for any chronic illness such as heart disease, irregular heartbeat, hypertension, diabetes, skin allergies or skin diseases, even if currently controlled by medication. Participants did not take any medications to treat their ADHD symptoms and had no comorbid Axis I diagnosis. Smokers were defined as individuals who have been smoking at least 5 cigarettes per day to up to 20 cigarettes per day for at least two years. Cigarette smoking history and habits were assessed with the California tobacco survey (Davis, 2005). Nicotine dependence was assessed with the Fagerström test for nicotine dependence (Fagerström, 1978). Each participant was asked to abstain from smoking overnight (i.e. at least 8 h) prior to participation, which was validated via self-report and with expired carbon monoxide using a portable CO analyzer (National Draeger). The standard cut-off level for participation in the study was 8 ppm prior to the NIRS. The level of nicotine per cigarette was verified by content description on the cigarette package. None of the participants were using or dependent on illicit drugs. Abstinence from drugs of abuse prior to and during participation in the study was verified with commercially available urine drug screens (Integrated E-Z Split Key Cups 10 Panel; Drugformation.com). There were no significant differences in sample characteristics between smokers with ADHD and control smokers (see Table 1).

Table 1
Sample characteristics.

Characteristics	ADHD ($N=6$)	Control ($N=6$)
Ages, years ($M \pm SD$)	22.5 ± 0.84	24.8 ± 2.49
Caucasian (%)	83.33	50
Education, years ($M \pm SD$)	12.0 ± 0.02	13.33 ± 1.63
Employed (%)	50	67
Number of cigarettes/day ($M \pm SD$)	10.75 ± 3.92	10.92 ± 6.51
Age started smoking regularly, years ($M \pm SD$)	17.17 ± 0.75	16.83 ± 2.93
Number of quit attempts ($M \pm SD$)	2.67 ± 1.63	2.83 ± 2.04
Nicotine per cigarette in mg ($M \pm SD$)	1.17 ± 0.14	1.00 ± 0.32
Fagerström test for nicotine dependence ($M \pm SD$)	3.33 ± 1.03	4 ± 2.00

2.2. Experimental procedure

The study was approved by the Institutional Review Board of the University of California, Irvine. The subjects were instructed to abstain from smoking overnight prior to the NIRS session. In the morning of the NIRS measurements, each participant was tested for carbon monoxide, breath alcohol and illicit drug use via urine drug screen. The study protocol was performed on an outdoor patio. Participants sitting outside had their shoulders against a wall and faced a large sun-block umbrella arranged at a 45° angle, with the concave side in front of them to reduce outdoor light interference with our acquisition. The NIRS head band was placed on the subject's forehead, held in place with an elastic band slightly attached to prevent vasoconstriction and covered with aluminum foil to reflect outdoor light. Participants also wore a breathing belt to detect variations in the breathing rate and smoking anomalies. The session started with approximately 2 min of relaxation (baseline). Measurements were taken over four time intervals: (1) two minutes prior to lighting a cigarette; (2) during smoking (start-to-end) lasting approximately 4 min; (3) during an exhaled breath hold after smoking (average duration 24 s and standard deviation of 10.65 in smokers with ADHD and 31 s with a standard deviation of 13.57 in control smokers); and (4) an additional 2 min after smoking.

2.3. Near-infrared spectroscopy

A single channel Oximeter (model 96208, ISS Inc., Champaign, IL) was used, which operates at a modulation frequency of 110 MHz and a cross-correlation frequency of 6 kHz, with 8 light sources, 4 emitting light at 690 nm, and 4 at 830 nm. Light intensity was modulated at a frequency of 9.76 Hz, providing an acquisition frequency of 10 data points per second.

Light sources were arranged at multiple distances ranging from 2.40 cm to 3.99 cm from the photon-multiplier tube (PMT) detector, in a linear way and encased in a silicon head band for optimal contact with the subject's forehead. Before measuring, the sensor was calibrated on a silicon block with optical properties comparable to those of the human brain. Similar to previous research (Safonova et al., 2004), measurements were performed on the left forehead of each subject.

2.4. Optical data analysis

The Oximeter provided a calculated measure of light intensity modulation, demodulation, from which values of the absorption μa and reduced scattering $\mu s'$ coefficients and phase delay were calculated. From these values the physiological quantities of HbO_2 and HHb were reconstructed as a function of wavelength (690 nm and 830 nm) and followed the frequency-domain multiple-distanced method (Gratton et al., 1997). Time series data were low pass filtered and the grand average of the initial baseline period was subtracted to reference zero change at baseline. Specifically, we applied a finite impulse response, FIR, filter with a zero phase delay. The filter kernel is defined by an algorithm implemented in the BoxyRead software. The implementation has a left–right symmetry and proceeds according to the recursion coefficient. We used a low band pass coefficient in the order of 0.8, which effectively suppresses all frequencies below 1 s. In addition, we removed signal frequencies due to systemic changes. Specifically the heart and breathing frequencies were removed according to the procedure explained in Gratton and Corballis (1995).

2.5. Statistical analysis

HbO_2 and HHb were analyzed with a 2 group (ADHD versus controls) and 4 time point (before smoking, during smoking, during breath hold, and after smoking) linear mixed model analysis of variance