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Interactive effects of chronic cigarette smoking and age on hippocampal volumes

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ABSTRACT

Background: Previous cross-sectional MRI studies with healthy, young-to-middle-aged adults reported no significant differences between smokers and non-smokers on total hippocampal volume. However, these studies did not specifically test for greater age-related volume loss in the total hippocampus or hippocampal subregions in smokers, and did they did not examine relationships between hippocampal and subfield volumes and episodic learning and memory performance.
Methods: Healthy, young-to-middle-aged (45 ± 12 years of age) smokers ($n = 39$) and non-smokers ($n = 43$) were compared on total hippocampal and subfield volumes derived from high-resolution 4 Tesla MRI, emphasizing testing for greater age-related volume losses in smokers. Associations between hippocampal volumes and measures of episodic learning and memory were examined.
Results: Smokers showed significantly smaller volumes, as well as greater volume loss with increasing age than non-smokers in the bilateral total hippocampus and multiple subfields. In smokers, greater pack-years were associated with smaller volumes of the total hippocampus, presubiculum, and subiculum. In the entire cohort, performance on measures of learning and memory was related to larger total hippocampal and several subfield volumes, predominately in the left hemisphere.
Conclusions: Chronic cigarette smoking in this young-to-middle aged cohort was associated with smaller total hippocampal and subfield volumes, which were exacerbated by advancing age. Findings also indicated an adverse smoking dose/duration response (i.e., pack-years) with total hippocampal and select subfield volumes. These hippocampal volume abnormalities in smokers may be related to the deficiencies in episodic learning and memory in young-to-middle-aged smokers reported in previous studies.

1. Introduction

An extensive body of research describes the deleterious effects of chronic cigarette smoking on human cardiac and pulmonary functions, vascular systems, as well as its carcinogenic properties, principally in the elderly (Ambrose and Barua, 2004; Bartal, 2001; Boudreaux et al., 2003; Casasola et al., 2002). However, beyond cardiovascular and cerebrovascular risk factors for stroke, little research has been devoted to effects of chronic smoking on human brain morphology, particularly in young-to-middle-aged adults (i.e., 25–60 years of age). This age range contains the greatest proportion of the population in the United States population (U.S. Census Bureau, 2012), and the greatest number of smokers. Specifically, the prevalence of smoking in the 25–60 age range is approximately 23% compared to 10% in those greater than 60 years of age (Dube et al., 2010). Previous cross-sectional magnetic resonance imaging (MRI) studies comparing brain morphological measures in young-to-middle-aged smokers and non-smokers (mean ages from 28 to 50 years of age) reported smokers showed smaller volumes and/or lower gray matter (GM) densities in the dorsolateral frontal cortex, anterior and posterior cingulate cortex, mesial temporal lobe, posterior parietal lobe, thalamus, cerebellum, and components of the basal ganglia, as well as thinner orbitofrontal cortex (Brody et al., 2004; Gallinat et al., 2006; Kuhn et al., 2010; Liao et al., 2010; Yu et al., 2011). Greater pack years were associated with smaller anterior frontal, temporal, and cerebellar GM volume (Brody et al., 2004; Gallinat et al., 2006), as well as thinner orbitofrontal cortex (Kuhn et al., 2010). Chronic cigarette smoking during middle-age is robustly associated with increased risk for Alzheimer's disease (AD) and other forms of dementia (Cataldo et al., 2010; Rusanen et al., 2010a, 2010b). Numerous MRI studies demonstrated significant volume loss in the total

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hippocampus (Chupin et al., 2009; Du et al., 2001; Fellgiebel et al., 2006; Pennanen et al., 2004; Schuff et al., 2001; Tapiola et al., 2006), and more recently, in hippocampal subfields (Apostolova et al., 2010a, 2012; Lim et al., 2012b; Mueller and Weiner, 2009), in those with mild cognitive impairment (MCI) and early-stage AD dementia. The rate of hippocampal atrophy in persons with MCI and AD is significantly greater than in cognitively normal elderly controls (Jack et al., 2000), and an increased rate of hippocampal atrophy in the cognitively normal elderly has been proposed as a neuroimaging biomarker of risk for MCI and early-stage AD dementia (Apostolova et al., 2012). Given that an abnormal rate of hippocampal atrophy in the elderly serves as a risk factor for MCI and early-stage AD dementia, it is of critical importance to determine if young-to-middle-aged chronic smokers manifest greater-than-normal age-related hippocampal volume loss. Previous cross-sectional MRI studies with young-to-middle-aged healthy, non-clinical cohorts reported no significant differences between smokers and non-smokers on total hippocampal volumes (Brody et al., 2004; Gallinat et al., 2006; Yu et al., 2011). However, these previous studies did not specifically test for greater age-related volume loss in the total hippocampus or hippocampal subregions (e.g., CA1, subiculum) in smokers, nor did they examine relationships between hippocampal and subfield volumes and episodic learning and memory performance. Accordingly, this study compared healthy, predominantly young-to-middle-aged smokers and non-smokers, on total hippocampal and subfield volumes derived from high-resolution MRI at 4 Tesla, and specifically tested for greater age-related volume loss in smokers.

We predicted that: (1) With increasing age, smokers show greater volume loss than non-smokers in total hippocampal volume, and in the CA1, CA2-3, CA4-dentate gyrus, and subiculum subfields; (2) Larger total hippocampal and subfield volumes are related to better performance on measures of learning and memory in the combined study cohort (i.e., smokers + non-smokers); (3) For smokers, greater pack-years and lifetime duration of smoking are related to smaller total hippocampal and subfield volumes.

2. Methods

2.1. Participants

Eighty-two healthy, community-dwelling participants [43 non-smokers (eight females) and 39 smokers (six females)], were recruited via posters, electronic billboards, and word-of-mouth. Participants were between the ages of 25 and 68 and all were employed at the time of study (see Table 1 for demographics). Participants provided written informed consent according to the Declaration of Helsinki, and the consent document and procedures were approved by the University of California San Francisco and the San Francisco VA Medical Center.

Primary inclusion/exclusion criteria are fully detailed elsewhere (Durazzo et al., 2012a). In summary, participants were screened for history of neurologic (e.g., seizure disorder, neurodegenerative disorder, demyelinating disorder, closed head trauma with loss of consciousness), general medical (e.g., hypertension, myocardial infarction, Type-1 or 2 diabetes, cerebrovascular accident), and psychiatric (i.e., mood, thought, anxiety, substance/alcohol use disorders) conditions known or suspected to influence neurocognition or brain neurobiology. All females were premenopausal, by self-report. All non-smoking participants never smoked, or smoked less than 40 cigarettes during their lifetime and used no cigarette/tobacco in the 10 years prior to study. All smoking participants were actively smoking at the time of assessment and smoked at least 10 cigarettes per day for 5 years or more, with no periods of smoking cessation greater than 1-month in the 5-years prior to study. No smoker was engaged in any pharmacological/behavioral smoking cessation program or used other forms of tobacco at the time of study.

2.2. Medical, psychiatric, substance, alcohol consumption assessment

Participants completed the screening section of the Structured Clinical Interview for DSM-IV Axis I disorders, Patient Edition, Version 2.0 (SCID-I/P; First et al., 1998), as well as an in-house questionnaire designed to screen for medical, psychiatric, neurological and developmental conditions that may affect neurocognition or brain neurobiology (see Durazzo et al., 2004). Participants completed standardized questionnaires assessing lifetime alcohol consumption (Lifetime Drinking History, LDH; Skinner and Sheu, 1982; Sobell et al., 1988) and substance use (in-house questionnaire assessing substance type, and quantity and frequency of use). From the LDH, we derived average number of drinks (defined as containing 13.6 g of pure ethanol) per month over 1-year prior to enrollment and average number of drinks per month over lifetime. Participants also completed self-report measures of depressive (Beck Depression Inventory, BDI; Beck, 1978) and anxiety symptomatology (State-Trait Anxiety Inventory, form Y-2, STAI; Spielberger et al., 1977). Smokers also completed a measure of nicotine dependence level (Fagerström Test for Nicotine Dependence, FTND; Heatherton et al., 1991), and provided information regarding the total number of cigarettes currently smoked per day, the number of years of smoking at the current level, and the total number of years of smoking over lifetime. From this information, pack years (i.e., (number of cigarettes per day/20) × total number of years of smoking) were calculated for smokers. Approximately 30% of smokers and non-smokers reported intermittent "recreational" use (i.e., ≤3 episodes/month) of cannabis or cocaine during late adolescence or early adulthood; there was no significant difference in frequency of substance use between smokers and non-smokers. Prior to assessment, participants' urine was tested for five common illicit substances (i.e., THC, opiates, PCP, cocaine, and amphetamines), and they were evaluated for recent ethanol consumption via breathalyzer. No participant was positive for the above common illicit substances or ethanol consumption at the time of assessment.

2.3. Magnetic resonance imaging (MRI) acquisition and processing

MRI data were acquired on a 4.0 Tesla Bruker MedSpec system using an 8-channel transmits-receive head coil (Siemens, Erlangen, Germany). A Magnetization Prepared Rapid Gradient (TR/TE/TI = 2300/3/950 ms, 7° flip angle, 1.0 mm × 1.0 mm × 1.0 mm resolution) sequence was used to acquire 3D sagittal T1-weighted images for morphological analyses. The publicly available Freesurfer (v5.1) segmentation and cortical surface reconstruction methods were used to obtain

Table 1
Demographic and clinical measures.

Variable	Non-smokers (n = 43)	Smokers (n = 39)
Age (years)	46.5 ± 11.0 min: 22.2; max: 68.8	43.3 ± 12.6 min: 23.7; max: 64.1
Education (years)	16.1 ± 2.1 min: 12; max: 20	14.8 ± 2.1* min: 12; max: 20
AMNART	119 ± 9	117 ± 6
% Male	81	84
% Caucasian	58	62
Beck Depression Inventory	2.7 ± 2.9	5.2 ± 4.2*
STAI-trait	32.2 ± 7.8	33.0 ± 6.8
1-year average drinks/month	13.8 ± 15.5	21.4 ± 19.6
Lifetime average drinks/month	17.7 ± 10.9	25.6 ± 13.8*
FTND	NA	4.7 ± 1.6
Cigarettes/day	NA	18.3 ± 6.9
Total lifetime years of smoking	NA	26.4 ± 11.5
Age started smoking daily	NA	20.0 ± 7.8 min: 11; max: 47
Pack years	NA	24.9 ± 15.9

Note. Mean ± standard deviation. AMNART: American National Adult Reading Test; FTND: Fagerstrom Test for Nicotine Dependence; STAI: State-Trait Anxiety Inventory, trait-score.
* $p < .05$.