Cigarette smoking is associated with cortical thinning in anterior frontal regions, insula and regions showing atrophy in early Alzheimer's Disease

Timothy C. Durazzo^{a, b}, Dieter J. Meyerhoff^{c, d}, Karmen K. Yoder^e

^a Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Rd., Stanford, CA 94305, USA

^b Mental Illness Research and Education Clinical Centers and Sierra-Pacific War Related Illness and Injury Study Center, VA Palo Alto Health Care System, 301 Miranda Ave., Palo Alto, CA 94304, USA

^c Department of Radiology and Biomedical Imaging, University of California, San Francisco, 505 Parnassus Ave, San Francisco, CA 94143

^d Center for Imaging of Neurodegenerative Diseases, San Francisco VA Medical Center, 4150 Clement St., 114M, San Francisco, CA 94121

^e Indiana University Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 550 N. University Blvd., Indianapolis, IN 46202, USA

Correspondence:

Timothy C. Durazzo

Mental Illness Research and Education Clinical Centers (151Y), War Related Illness and Injury

Study Centers, VA Palo Alto Health Care System

3801 Miranda Ave., Palo Alto, CA 94304

Phone: (650) 493-5000 x62982

Fax: (650) 852-3267

tdurazzo@stanford.edu; timothy.durazzo@va.gov

This is the author's manuscript of the article published in final edited form as:

Durazzo, T. C., Meyerhoff, D. J., & Yoder, K. K. (2018). Cigarette smoking is associated with cortical thinning in anterior frontal regions, insula and regions showing atrophy in early Alzheimer's Disease. Drug and Alcohol Dependence. https://doi.org/10.1016/j.drugalcdep.2018.08.009

Highlights

- Smokers showed cortical thinning in multiple brain regions relative to Non-Smokers.
- Greater cigarette pack years was related to thinner cortex in multiple regions.
- In Smokers, impulsivity and poorer decision-making was related to thinner cortex.

Abstract

Background: Magnetic resonance imaging studies of cigarette smoking-related effects on human brain structure primarily focused on cortical volumes. Much less is known about the effects of smoking on cortical thickness. Smokers and Non-smokers were compared on regional cortical thickness. We predicted smokers would demonstrate greater age-related thinning localized to anterior frontal regions that serve as nodes for the executive, salience, and emotional regulation networks (ESER regions) and those demonstrating significant atrophy in early Alzheimer's Disease (AD regions).

Methods: Non-smokers (n = 41) and smokers (n = 41), 22-70 years of age, completed a 4 Tesla MRI study. Regional cortical thickness was quantitated via FreeSurfer. In smokers, associations between smoking severity, decision-making, impulsivity, and regional cortical thickness were examined.

Results: Smokers demonstrated cortical thinning in the medial and lateral OFC, insula, entorhinal, fusiform, middle temporal, and Composite AD regions. In Smokers, greater pack-years were associated with thinner lateral OFC, middle temporal, inferior parietal, fusiform, precuneus, and Composite AD regions. In Smokers, poorer decision-making/greater risk taking was related to thinner cortices in caudal ACC, rostral middle frontal and superior frontal gyri,

and Composite ESER. Higher self-reported impulsivity was associated with thinner rostral and caudal ACC.

Conclusions: This study provides additional evidence that cigarette smoking is associated with thinner cortices in regions implicated in the development and maintenance of substance use disorders and in regions demonstrating significant atrophy in early AD. The novel structure-function relationships in Smokers further our understanding of the neurobiological substrates potentially underlying the neuropsychological abnormalities documented in smokers.

Keywords: Cigarette Smoking; Magnetic Resonance Imaging; Cortical Thickness; Decision-Making; Impulsivity; FreeSurfer

1. Introduction

The link between cigarette smoking and markedly increased risk for pulmonary, cardiac, and vascular disease as well as for multiple forms of cancer in humans is essentially indisputable (CDC, 2004). A growing body of evidence also indicates that smoking, in otherwise healthy individuals, is associated with neurobiological and neurocognitive abnormalities that are not directly related to the foregoing diseases (Azizian et al., 2009; Durazzo et al., 2014a; Durazzo et al., 2010; Durazzo et al., 2017; Sharma and Brody, 2009). Most magnetic resonance (MR) studies investigating the neurobiological consequences of cigarette smoking have focused on volume/density of cortical gray matter (GM) and/or subcortical nuclei (see Durazzo et al., 2010; Pan et al., 2013; Sutherland et al., 2016 for review). Smaller volumes or lower density in dorsal and ventromedial prefrontal cortex, orbitofrontal cortex, insula, thalamus, and cerebellum were

the most consistently reported findings (Durazzo et al., 2010; Pan et al., 2013; Sutherland et al., 2016); structural abnormalities in these regions are also apparent in alcohol and substance use disorders (see Buhler and Mann, 2011; Cadet et al., 2014 for review) The anterior frontal, insular, and subcortical regions that show structural abnormalities in smokers are critical nodes in the executive, salience, and emotional regulation networks (Seeley et al., 2007; Williams, 2016). Additionally, in smokers, studies have reported smaller volumes (Almeida et al., 2011; Almeida et al., 2008; Peng et al., 2018) in adults and elders, greater longitudinal volume loss over 2 years in elders (Durazzo et al., 2012), and accelerated age-related volume loss in middleaged adults (Durazzo et al., 2013a; Durazzo et al., 2017) in cortical and subcortical regions that show atrophic changes in those with mild cognitive impairment and early-stage Alzheimer's Diseasedisease (Vemuri et al., 2010). Correspondingly, chronic smoking during adulthood is associated with significantly elevated risk for Alzheimer's Diseasedisease and related neuropathological changes (see Durazzo et al., 2014a for review). The cumulative body of research suggests chronic smoking-related structural abnormalities also show considerable overlap with regions that manifest atrophic changes in alcohol/substance use disorders and Alzheimer's Diseasedisease.

While most MR studies have investigated the consequences of smoking on cerebral volume, fewer studies have examined smoking-related effects on cortical thickness. Cortical thickness is believed to reflect the number and density of cells in a column (Rakic, 1988; 2008) and/or represent neuronal cell body size, the number of spines and synapses, and the degree of myelination (Eickhoff et al., 2005; Fjell and Walhovd, 2010). Cortical thickness is genetically and phenotypically distinct from cortical surface area and volume (Kremen et al., 2010; Panizzon et al., 2009; Winkler et al., 2010), and it is related to neurocognition in healthy adults and

adolescents (Choi et al., 2008; Dickerson et al., 2008; Fjell et al., 2006; Schilling et al., 2013; Walhovd et al., 2006) and those with a cocaine use disorder (Makris et al., 2008a). Cortical thickness is reputed to be more sensitive to neurodegenerative processes than cortical volumes (Hutton et al., 2009); therefore, this morphometric may increase the ability to detect more subtle structural abnormalities than volumes or density measures and/or be differentially affected by addictive disorders compared to volumes and surface area (Durazzo et al., 2011b; Wang et al., 2016). Taken together, cortical thickness may serve as a proxy for the integrity of cortical cytoarchitecture (Makris et al., 2007). Kuhn and colleagues (Kuhn et al., 2010) reported that adult smokers had thinner left medial orbitofrontal cortex (OFC) than never-smokers. Karama and colleagues (Karama et al., 2015) reported wide-spread reduction of thickness across the cortex, with the greatest thinning in anterior frontal regions in elder active smokers relative to never smokers, after adjusting for vascular risk factors. In a sample of late adolescent/young adults, Li and associates (Li et al., 2015) reported that smokers demonstrated significant cortical thinning in the left caudal anterior cingulate cortex (ACC), right lateral OFC, left insula, left middle temporal gyrus, right inferior parietal lobule, and right parahippocampus. In the above studies, greater pack-years was associated with thinner cortices in the regions that also showed significantly thinner cortices in smokers relative to never-smokers. However, associations between regional cortical thickness and clinically relevant aspects of decision-making and impulsivity, which are key cognitive components in the initiation and maintenance of addictive disorders (Fineberg et al., 2010; Verdejo-Garcia and Bechara, 2009), were not examined in these studies.

The risk for smoking-related diseases increases with years of smoking (CDC, 2004), which is inextricably linked to age. In healthy adults, increasing age is associated with declines

in regional cortical thickness (Fjell et al., 2015; Storsve et al., 2014). In the few previous studies investigating smoking-related effects on cortical thickness, mean thickness differences were examined between smokers and never-smokers. While this approach permitted testing for the effect of smoking status (i.e., smoker vs. never-smoker) collapsed across the age range of the participants, no study specifically tested for a smoking status by age interaction. Our previous neuroimaging studies showed that, in healthy participants 25-70 years of age, smokers had both lower mean values and greater age-related declines of anterior frontal brain metabolite concentrations (N-acetylaspartate and glutamate) and hippocampal and subcortical volumes (Durazzo et al., 2016c; Durazzo et al., 2013a; Durazzo et al., 2017). In these studies, greater cigarette pack-years was related to lower metabolite levels and smaller regional volumes. The greater age-related declines apparent in smokers suggest that chronic smoking amplified the effects of normal aging on multiple aspects of neurobiology. These neurobiological abnormalities may influence reward processing and response to smoking cessation interventions via alterations of the integrity of structural and/or functional connectivity in frontolimbic and/or frontostriatal circuitry (Froeliger et al., 2015; Hong et al., 2009; Li et al., 2017; Sutherland et al., 2013; Sutherland et al., 2016; Sweitzer et al., 2016). Based on previous neuroimaging findings from our group and others, we predicted that adult smokers would demonstrate greater agerelated cortical thinning and lower mean thickness in anterior frontal regions that serve as nodes for the executive, salience, and emotional regulation networks (hereafter referred to as ESER regions) as well as in posterior regions that show significant atrophy in early-stage Alzheimer's Diseasedisease (hereafter referred to as AD regions). In smokers, we hypothesized that higher pack-years are related to thinner cortices in ESER and AD regions. We also predicted that poorer

performance on measures of decision-making/risk-taking and impulsivity are associated with thinner cortices in ESER regions of smokers.

2. Methods

2.1 Participants

Eighty-two healthy, community-dwelling participants [41 non-smokers (seven females) and 41 smokers (six females)] were recruited via electronic billboards and word-of-mouth. Participants were between the ages of 22 and 70 (see Table 1 for demographics). Participants gave written informed consent according to the Declaration of Helsinki, and all procedures were approved by the University of California San Francisco and the San Francisco VA Medical Center.

Detailed inclusion/exclusion criteria are described elsewhere (Durazzo et al., 2011a). In summary, participants were screened for the following: history of neurologic (e.g., seizure disorder, neurodegenerative disorder, demyelinating disorder, closed head trauma with loss of consciousness), and general medical (e.g., hypertension, myocardial infarction, Type-1 or 2 diabetes, cerebrovascular accident, any form of cancer) and psychiatric (i.e., mood, thought, anxiety, trauma and stressor-related, substance/alcohol use disorders) conditions known or suspected to influence neurocognition and/or brain neurobiology. Non-smoking participants never smoked (n = 36) or smoked less than 40 cigarettes during their lifetime and used no tobacco products for at least 10 years prior to study (n = 5). All smoking participants were actively smoking at the time of assessment, smoked at least 10 cigarettes/day for 5 years or more, and had no periods of smoking cessation greater than 1 month in the 5 years prior to study with no concurrent use of other tobacco products. No smoker was engaged in any pharmacological and/or behavioral smoking cessation program at the time of study.

2.2 Medical, psychiatric, substance, alcohol consumption and behavioral 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 neurobiology (see Durazzo et al., 2004). Participants completed standardized questionnaires assessing substance use [in-house questionnaire assessing substance type, quantity and frequency of use (Abe et al., 2013)] and lifetime alcohol consumption [Lifetime Drinking History, LDH; (Skinner and Sheu, 1982; Sobell et al., 1988)]. From the LDH, average number of drinks per month over lifetime (one drink defined as containing 13.6 grams of pure ethanol) was calculated. 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 completed a measure of nicotine dependence level [Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991)], self-reported the number of cigarettes currently smoked per day, and number of years of smoking over their lifetime. Pack-years (number of cigarettes per day/20) x total number of years of smoking was calculated for smokers. An equivalent frequency of Smokers and Non-Smokers (30%) reported intermittent "recreational" use (i.e., ≤ 3 episodes/month) of cannabis or cocaine during late adolescence or early adulthood. Prior to assessment, participants' urine was tested for five common illicit substances (THC, opiates, PCP, cocaine, amphetamines), and participants were breathalyzed for recent ethanol consumption. No participant was positive for the above common substances or ethanol at the time of assessment. Smokers and Non-Smokers completed the Iowa Gambling Task, [IGT (Bechara, 2007)], a task-based measure of decision-making and risk-taking, and the Barrett

Impulsivity Scale-11 [BIS-11 (Patton et al., 1995)], a self-report measure of aspects of trait impulsivity.

2.3 Magnetic Resonance Imaging (MRI) acquisition and processing

Morphological MRI data were acquired on a 4.0 Tesla Bruker MedSpec system using an 8-channel transmit-receive head coil (Siemens, Erlangen, Germany). A Magnetization Prepared Rapid Gradient (TR/TE/TI = 2300/3/950 ms, 7° flip angle, 1.0 x 1.0 x 1.0 mm³ 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 thickness for 34 bilateral regions (mm) and total intracranial volume (ICV; mm³) (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2004; Fischl et al., 1999). All segmented subcortical and parcellated cortical T1-weighted images were visually inspected by one of the authors (TCD) for accuracy; any errors in segmentation/parcellation were manually edited, reprocessed, and reinspected as previously described (Durazzo et al., 2014c). The final segmented subcortical and parcellated cortical volumes passed all quality requirements (Durazzo et al., 2014c). Analyses focused on cortical components that serve as nodes for the ESER (Seeley et al., 2007; Williams, 2016) and included the bilateral rostral and caudal ACC, medial and lateral OFC, rostral and caudal middle frontal gyri, and superior frontal gyri. An ESER composite thickness was created by calculating the surface area-weighted average of all ESER ROIs (Durazzo et al., 2014c). AD ROIs included the bilateral entorhinal cortex, fusiform gyri, inferior temporal, inferior parietal lobule, isthmus and posterior cingulate, and precuneus. An AD composite thickness was created by calculating the surface area-weighted average of all AD ROIs (Durazzo et al., 2014c).

2.4 Statistical Analyses

2.4.1 Demographic and clinical variables. Demographic and clinical variables were compared between smokers and non-smokers with *t*-tests and Fisher's Exact Test where indicated.

2.4.2 Comparisons of Smokers and Non-smokers on regional ESER and AD thickness. To test our hypothesis of greater age-related regional cortical thinning in smokers, we employed generalized linear modeling (GENLIN) and specifically tested for a smoking status (smoker vs. non-smoker) by age interaction. In preliminary analyses comparing smokers and non-smokers, no consistent pattern emerged for lateralized differences in the ROIs; therefore, results for the average of the left and right hemisphere for each ESER, AD, and Non-ESER/AD ROIs are presented. Dependent measures were ROI thickness, and covariates included age, education, BDI score, ICV, average lifetime drinks/month (smokers and non-smokers were different on education, BDI score, and average lifetime drinks/month; see Table 1 and section 3.1. below). Although cortical thickness is reported to not show the same strong magnitude of relationships with ICV as surface area and volume (e.g., Kremen et al., 2010; Panizzon et al., 2009), cortical thickness was significantly inversely related to ICV in our previous studies of individuals with alcohol use disorder and healthy controls (Durazzo et al., 2013b; Durazzo et al., 2011b). Main effects and interactions between smoking status and age and follow-up t-tests (two-tailed) were considered significant at p < .05. In all previous neuroimaging-based reports with this cohort (Durazzo et al., 2016c; Durazzo et al., 2013a; Durazzo et al., 2017), we conservatively corrected *t*-tests for multiple comparisons. Given our *a priori* predictions and our consistent findings of neurobiological and neurocognitive abnormalities in smokers in the ROIs investigated in this study, follow-up *t*-tests were considered statistically significant at p < .05, uncorrected. Effect

sizes were calculated with Cohen's d (Cohen, 1988) for statistically significant differences in ROI thickness between smokers and non-smokers.

2.4.3 Comparisons of Smokers and Non-smokers on non-ESER/AD ROI thickness. Smokers and Non-Smokers were compared on regions outside the specified ESER and AD ROIs to determine if smoking-related effects on cortical thickness were localized to ESER and AD ROIs or were more widely distributed. GENLIN was used for these comparisons, and, consistent with analyses of Smokers and Non-Smokers on ESER and AD ROIs, we specifically tested for a smoking status (smoker vs. non-smoker) by age interaction and employed the same covariates. Main effects and interactions between smoking status and age and follow-up *t*-tests (two-tailed) were considered significant at p < .05 in these exploratory analyses. The following cortical regions were compared: banks of superior temporal gyrus, cuneus, frontal pole, lingual, paracentral, pars opercularis, pars triangularis, pericalcarine, post central, precentral, superior parietal, superior temporal, and transverse temporal cortices.

2.4.4 Associations between ESER, AD, and non-ESER/AD ROI thickness and smoking severity measures. In Smokers, associations between the ESER, AD, and Non-ESER/AD ROI thickness and cigarette pack-years (measure of exposure magnitude) and FTND score (measure of nicotine dependence level) were examined by linear regression (partial correlations reported) adjusting for age, education, and ICV. A two-tailed p < .05 was considered statistically significant, and only associations of at least moderate magnitude (i.e., $r \ge |0.30|$) were reported.

2.4.5 Associations between ESER, AD, and Non-ESER/AD ROI thickness and decisionmaking/risk-taking and impulsivity in Smokers and Non-Smokers. Associations of ESER and AD ROI thickness and performance on the IGT Total Score (raw score) and BIS-11 total score, attentional impulsivity, motor impulsivity, and non-planning impulsivity were separately

examined in Smokers and Non-Smokers with linear regression (partial correlations reported) adjusted for age, education, and ICV. A two-tailed p < .05 was considered statistically significant, and only associations of at least moderate magnitude (i.e., $r \ge |0.30|$) were reported. See Durazzo et al. (2016c) for comparisons of Smokers and Non-Smokers from this cohort on the IGT and BIS-11, in which Smokers performed more poorly on the IGT (indicative of poorer decision-making/greater risk taking) and showed higher BIS-11 scores (indicative of greater impulsivity) than Non-Smokers.

3. Results

3.1 Participant demographics and clinical variables

Smokers and Non-Smokers were equivalent on age, sex, percent of Caucasians, and level of anxiety symptomatology. Smokers had significantly lower educational level, higher BDI scores, and consumed more average lifetime alcoholic drinks per month (all p < .05). Although statistically different between groups, the average BDI score for both groups was in the normal range (i.e., < 10) and well below the cutoff for mild depressive symptomatology (Richter et al., 1998). Participant alcohol consumption did not approach a hazardous level [see (McKee et al., 2007; Mertens et al., 2005)] (see Table 1). All females were pre-menopausal, by self-report.

3.2 Comparisons of Smokers and Non-Smokers on ESER and AD ROI cortical thickness

Models containing smoking status, age, and ICV were significant predictors of thickness in the medial OFC [$\chi^2(3) = 9.56$, p = .023], lateral OFC [$\chi^2(3) = 13.5$, p = .004], entorhinal cortex [$\chi^2(3) = 14.3$, p = .003], fusiform gyrus [$\chi^2(3) = 39.4$, p < .001], and middle temporal gyrus [$\chi^2(3) = 37.2$, p < .001]; greater age was related to thinner cortex, and larger ICV was associated with thicker cortex in these ROIs (all p < .01). The model with smoking status, age,

and lifetime average drinks per month showed they were significant predictors of insula thickness [$\chi^2(3) = 35.3$, p < .001]; greater age and lifetime average drinks per month were related to thinner insular cortex (all p < .05). The model with smoking status, age, and education showed them to be predictors of Composite AD ROI thickness [$\chi^2(3) = 44.3$, p < .001]; greater age was related to thinner Composite AD ROIs and higher education, and ICV was associated with thicker Composite AD ROIs (all p < .05). Smokers demonstrated thinner cortices than Non-Smokers in all above ROIs (see Fig. 1 and 2). BDI score was not a significant predictor of thickness in any region. The smoking status x age interactions were not significant for any ROI examined.

3.3 Comparisons of Smokers and Non-Smokers on Non-ESER and AD cortical ROI thickness

No significant smoking status x age interactions or main effects for smoking status were observed for any Non-ESER/AD ROI.

3.4 Associations of pack-years and nicotine dependence and regional thickness in Smokers

3.4.1 ESER and AD ROIs. In Smokers, higher pack-years was related to thinner cortices in the middle temporal (r = -0.50, p = .001; see Fig. 3), inferior parietal (r = -0.42, p = .010), fusiform (r = -0.41, p = .013), precuneus (r = -0.37, p = .024), lateral OFC (r = -0.33, p = .047), and composite AD (r = -0.40, p = .013) ROIs. No significant associations were observed between FTND score and ESER or AD ROIs.

3.4.2 Non-ESER/AD ROIs. There were no significant associations between pack-years and FTND score for any region.

3.5 Associations of measures of decision-making and impulsivity with regional thickness in Smokers and Non-Smokers

3.5.1 ESER and AD ROIs. In Smokers, lower IGT Net Total Score (indicative of poorer decision-making/lower risk-taking) was associated with thinner cortices in the superior frontal gyrus (r = 0.51, p = .005; see Fig. 4), caudal ACC (r = 0.44, p = .020), rostral middle frontal gyrus (r = -0.43, p = .022), and composite ESER (r = 0.43, p = .022). On the BIS-11, higher non-planning impulsivity (r = -0.35, p = .046), motor impulsivity (r = -0.38, p = .028), and BIS-11 total score (r = -0.43, p = .022) were related to thinner rostral ACC, and higher non-planning impulsivity was associated with thinner caudal ACC (r = -0.37, p = .030). The associations between the IGT, BIS-11, and above ROIs largely showed equivalent magnitudes for the left and right hemisphere for both groups (data not shown). There were no significant relationships between IGT, BIS-11, and ESER or AD ROI thickness in Non-Smokers.

3.5.2 Non-ESER/AD. There were no significant associations between IGT Net Total Score, BIS-11, and cortical thickness in the Non-ESER/AD ROIs in Smokers and Non-Smokers.

4. Discussion

The primary findings of this 4 Tesla quantitative MRI study were: 1) Otherwise healthy adult Smokers demonstrated significant cortical thinning compared to Non-Smokers in the medial and lateral OFC, insula, entorhinal, fusiform, middle temporal, and Composite AD ROIs. Smokers and Non-Smokers did not show statistically significant differences in thickness in areas outside ESER and AD ROIs. 2) In Smokers, greater pack-years were associated with thinner cortices in the lateral OFC, middle temporal, inferior parietal, fusiform, precuneus, and Composite AD ROIs. 3) In Smokers, poorer decision-making/lower risk taking was related to thinner cortices in the caudal ACC, rostral middle frontal gyrus, superior frontal gyrus, and

Composite ESER. Higher measures of impulsivity were associated with thinner cortices in the rostral and caudal ACC in Smokers.

The overall pattern of findings indicates the regional cortical thinning and associations with pack-years demonstrated by this group of smokers were limited to ESER and AD ROIs. These results are highly consistent with the few previous published studies of smoking-related effects on regional cortical thickness in non-clinical populations (Karama et al., 2015; Kuhn et al., 2010; Li et al., 2015) and also congruent with studies investigating the effects of smoking on regional brain volumes (see Durazzo et al., 2010; Pan et al., 2013; Sutherland et al., 2016). Contrary to predictions, smokers did not show greater age-related cortical thinning in any ROI, unlike the greater age-related decline in hippocampal and subcortical volumes (Durazzo et al., 2013a; Durazzo et al., 2017) and brain metabolites (Durazzo et al., 2016c) previously observed in this cohort. As this study excluded individuals with clinically significant smoking-related morbidity, it is possible that the age-related effects on cortical thickness were underestimated in this otherwise healthy cohort (Durazzo et al., 2014a), and/or the age range was not sufficient to yield a smoking status by age interaction.

In ESER regions, Smokers showed thinning of the medial and lateral OFC and insula. Collectively, the OFC is implicated in appraisal of stimulus saliency and representation of reward magnitude, self-monitoring, emotional and impulse regulation, and aspects of decisionmaking and executive skills (Fettes et al., 2017; Kringelbach and Rolls, 2004; Rolls and Grabenhorst, 2008). The insula is involved in monitoring internal physiological states/sensations (i.e., interoception), adjustment of attentional control based on internal physiological states (Naqvi and Bechara, 2010; Paulus, 2007), and is a major node in the salience network (Williams, 2016). A double blind, placebo-controlled trial of repetitive transcranial magnetic stimulation

found that high frequency stimulation (one session/day for 13 days) to the bilateral insula and dorsolateral prefrontal cortex was associated with a smoking cessation rate of 44% immediately after treatment and 33% cessation rate in the 6 months following the treatment (Dinur-Klein et al., 2014). In AD regions, Smokers demonstrated thinner cortices in the entorhinal, fusiform, and middle temporal gyrus as well as across the collective AD ROIs. These regions subserve aspects of face and body recognition, color processing, word recognition (left hemisphere), and declarative and spatial memory (Grill-Spector and Weiner, 2014; Kolb and Whishaw, 2009). Compromised structural integrity of the ESER and AD cortical regions, as indicated by the reduced thickness, may contribute to the abnormalities observed in smokers in mood regulation, cue reactivity, impulse control, decision-making, learning and memory, executive skills (Durazzo et al., 2016c; Durazzo et al., 2010, 2011a; Fergusson et al., 2003), and to the altered functional connectivity (Fedota and Stein, 2015).

Greater pack-years showed moderate magnitude associations with thinner cortices in the lateral OFC, middle temporal, inferior parietal, fusiform, precuneus, and composite AD ROIs. The lateral OFC, middle temporal, fusiform, and Composite AD thicknesses were significantly reduced in Smokers, which suggests a cigarette dose/duration-response relationship. No significant associations were observed between pack-years and thickness in areas outside the ESER and AD ROIs. Increased smoking-related cerebral oxidative stress (see Durazzo et al., 2016a; Durazzo et al., 2016b; Durazzo et al., 2014a; Durazzo et al., 2014b) and/or chronic nicotine exposure (see Durazzo et al., 2014a; Sutherland et al., 2016) are hypothesized to be fundamental mechanisms contributing to the structural and other neurobiological abnormalities observed in smokers. Replication in larger samples is required to determine if ESER and AD thickness show selective vulnerability to cigarette smoking and if premorbid or comorbid factors

not investigated in this study also contribute to the altered structural integrity observed in these regions.

In Smokers, poorer performance on the IGT (indicative of worse decision-making/greater risk-taking) was related to thinner cortices in the superior frontal gyrus, caudal ACC, rostral middle frontal gyrus, and composite ESER. These results are congruent with findings that tissue integrity of the dorsolateral and ventral medial prefrontal cortex and caudal ACC is related to performance on the IGT and other tasks/situations that require adjustment of goal-directed activity based on current environmental contingencies and anticipated future consequences (Bush et al., 2002; Clark et al., 2003; Fellows and Farah, 2005; Mega and Cummings, 1994). Higher aspects of self-reported impulsivity were related to thinner rostral and caudal ACC, which is consistent with the role of the ACC in monitoring and regulation of behavior and emotions (Bush et al., 2000; Goodkind et al., 2015; Williams, 2016). There were no significant associations between the IGT and BIS-11 and regional cortical thickness in Non-Smokers. The variance on the IGT and BIS-11 in Non-Smokers was relatively low, which appears to have restricted the range on these measures and likely dampened the magnitude of the associations between these measures and likely dampened the magnitude of the associations between these measures and regional cortical thickness in this group.

This study has limitations that may affect the generalizability of the findings. Undocumented premorbid/comorbid group differences in lifestyle or subclinical biomedical conditions (e.g., poor diet and nutrition, lack of exercise, subclinical pulmonary or cardiovascular dysfunction) and/or genetic polymorphisms (Mon et al., 2013) may have influenced the results. Additionally, the small number of females precluded assessment of sex effects.

5. Conclusions

This study provides additional evidence that cigarette smoking is associated with cortical thinning in regions implicated in the development and maintenance of substance use disorders as well as those that show significant atrophy in mild cognitive impairment and early AD. The novel structure-function relationships apparent in Smokers offer further insight into the neurobiological substrates related to the multiple neuropsychological abnormalities documented in cigarette smokers across adulthood. Smoking-related diseases kill at least 6 million individuals annually across the globe (WHO, 2015), and smoking is linked to increased risk for the development of Alzheimer's Diseasedisease and related neuropathology (Durazzo et al., 2016a; Durazzo et al., 2016b; Durazzo et al., 2014a). Studies with elder adults suggest that at least partial recovery of regional morphological abnormalities is possible with extended smoking cessation (Almeida et al., 2011; Karama et al., 2015). Therefore, longitudinal research on the effects of chronic smoking on brain micro-and-macrostructural integrity, biochemistry, functional and structural connectivity, and their functional correlates is essential to inform the development of new treatment modalities to promote sustained smoking cessation (Ding et al., 2018; Durazzo et al., 2014a; Sweitzer et al., 2016).

Author Disclosures

Role of the Funding Source

The study sponsors (Department of Veteran Affairs, National Institutes of Health and Department of Defense) had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Contributors

Dr. Durazzo was responsible for study concept and design, participant recruitment and screening, clinical and behavioral assessments, MR data acquisition, MR data processing, statistical analyses, data interpretation and writing the manuscript. Drs. Meyerhoff and Yoder were involved in data interpretation, manuscript editing, and contributed significant intellectual content to the manuscript. All authors contributed to and approved the final version of the manuscript.

Conflict of Interest

No conflict declared.

Acknowledgements

This material is the result of work supported by the National Institute on Drug Abuse (DA24136 to TCD), the Department of Defense (W81XWH-05-2-0094 to TCD), Department of Veteran Affairs (RX002303 to TCD), the National Institute on Alcohol and Alcoholism (AA10788 to DJM), and by resources and the use of facilities at the Palo Alto Veterans Administration Health Care System, Palo Alto, CA and San Francisco Veterans Administration Medical Center, San Francisco, CA. We thank Drs. Anderson Mon and Donna Murray for assistance in MR data acquisition of study participants. We also wish to extend our gratitude to the study participants, who made this research possible.

References

- Abe, C., Mon, A., Hoefer, M.E., Durazzo, T.C., Pennington, D.L., Schmidt, T.P., Meyerhoff,
 D.J., 2013. Metabolic abnormalities in lobar and subcortical brain regions of abstinent
 polysubstance users: Magnetic resonance spectroscopic imaging. Alcohol Alcohol. 48, 543-551.
- Almeida, O.P., Garrido, G.J., Alfonso, H., Hulse, G., Lautenschlager, N.T., Hankey, G.J., Flicker, L., 2011. 24-month effect of smoking cessation on cognitive function and brain structure in later life. Neuroimage 55, 1480-1489.
- Almeida, O.P., Garrido, G.J., Lautenschlager, N.T., Hulse, G.K., Jamrozik, K., Flicker, L., 2008. Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. Am. J. Geriatr. Psychiatry 16, 92-98.
- Azizian, A., Monterosso, J., O'Neill, J., London, E.D., 2009. Magnetic resonance imaging studies of cigarette smoking. Handb. Exp. Pharmacol. 192, 113-143.
- Bechara, A., 2007. Iowa Gambling Task, professional manual. Psychological Assessment Resources. Inc., Lutz, FL.
- Beck, A.T., 1978. Depression inventory. Center for Cognitive Therapy, Philadelphia.
- Buhler, M., Mann, K., 2011. Alcohol and the human brain: A systematic review of different neuroimaging methods. Alcohol. Clin. Exp. Res. 35, 1771-1793.
- Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215-222.
- Bush, G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., Rosen, B.R., 2002.Dorsal anterior cingulate cortex: A role in reward-based decision making. Proc. Natl. Acad. Sci. U.S.A. 99, 523-528.

- Cadet, J.L., Bisagno, V., Milroy, C.M., 2014. Neuropathology of substance use disorders. Acta Neuropathol. 127, 91-107.
- Choi, Y.Y., Shamosh, N.A., Cho, S.H., DeYoung, C.G., Lee, M.J., Lee, J.M., Kim, S.I., Cho, Z.H., Kim, K., Gray, J.R., Lee, K.H., 2008. Multiple bases of human intelligence revealed by cortical thickness and neural activation. J. Neurosci. 28, 10323-10329.
- Clark, L., Manes, F., Antoun, N., Sahakian, B.J., Robbins, T.W., 2003. The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. Neuropsychologia 41, 1474-1483.
- Cohen, J., 1988. Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates, Hillsdale, NJ.
- Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9, 179-194.
- Dickerson, B.C., Fenstermacher, E., Salat, D.H., Wolk, D.A., Maguire, R.P., Desikan, R.,
 Pacheco, J., Quinn, B.T., Van der Kouwe, A., Greve, D.N., Blacker, D., Albert, M.S.,
 Killiany, R.J., Fischl, B., 2008. Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths.
 Neuroimage 39, 10-18.
- Ding, X., Salmeron, B.J., Wang, J., Yang, Y., Stein, E.A., Ross, T.J., 2018. Evidence of subgroups in smokers as revealed in clinical measures and evaluated by neuroimaging data: A preliminary study. Addict Biol. Epub ahead of print.
- Dinur-Klein, L., Dannon, P., Hadar, A., Rosenberg, O., Roth, Y., Kotler, M., Zangen, A., 2014. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the

prefrontal and insular cortices: A prospective, randomized controlled trial. Biol. Psychiatry 76, 742-749.

- Durazzo, T., Insel, P.S., Weiner, M.W., 2012. Greater regional brain atrophy rate in healthy elders with a history of cigarette smoking. Alzheimers Dement. 8, 513-519.
- Durazzo, T.C., Gazdzinski, S., Banys, P., Meyerhoff, D.J., 2004. Cigarette smoking exacerbates chronic alcohol-induced brain damage: A preliminary metabolite imaging study. Alcohol. Clin. Exp. Res. 28, 1849-1860.
- Durazzo, T.C., Korecka, M., Trojanowski, J.Q., Weiner, M.W., R, O.H., Ashford, J.W., Shaw, L.M., 2016a. Active cigarette smoking in cognitively-normal elders and probable Alzheimer's Disease is associated with elevated cerebrospinal fluid oxidative stress biomarkers. J. Alzheimers Dis. 54, 99-107.
- Durazzo, T.C., Mattsson, N., Weiner, M.W., 2016b. Interaction of cigarette smoking history with APOE genotype and age on amyloid level, glucose metabolism, and neurocognition in cognitively normal elders. Nicotine Tob. Res. 18, 204-211.
- Durazzo, T.C., Mattsson, N., Weiner, M.W., 2014a. Smoking and increased Alzheimer's disease risk: A review of potential mechanisms. Alzheimers Dement. 10, S122-S145.
- Durazzo, T.C., Mattsson, N., Weiner, M.W., Korecka, M., Trojanowski, J.Q., Shaw, L.M., 2014b. History of cigarette smoking in cognitively-normal elders is associated with elevated cerebrospinal fluid biomarkers of oxidative stress. Drug Alcohol Depend. 142, 262-268.
- Durazzo, T.C., Meyerhoff, D.J., Mon, A., Abe, C., Gazdzinski, S., Murray, D.E., 2016c. Chronic cigarette smoking in healthy middle-aged individuals is associated with decreased regional brain N-acetylaspartate and glutamate levels. Biol. Psychiatry 79, 481-488.

- Durazzo, T.C., Meyerhoff, D.J., Nixon, S.J., 2010. Chronic cigarette smoking: Implications for neurocognition and brain neurobiology. Int. J. Environ. Res. Public Health 7, 3760-3791.
- Durazzo, T.C., Meyerhoff, D.J., Nixon, S.J., 2011a. A comprehensive assessment of neurocognition in middle-aged chronic cigarette smokers. Drug Alcohol Depend. 122, 105-111.
- Durazzo, T.C., Meyerhoff, D.J., Nixon, S.J., 2013a. Interactive effects of chronic cigarette smoking and age on hippocampal volumes. Drug Alcohol Depend. 133, 704-711.
- Durazzo, T.C., Meyerhoff, D.J., Yoder, K.K., Murray, D.E., 2017. Cigarette smoking is associated with amplified age-related volume loss in subcortical brain regions. Drug Alcohol Depend. 177, 228-236.
- Durazzo, T.C., Mon, A., Gazdzinski, S., Meyerhoff, D.J., 2013b. Chronic cigarette smoking in alcohol dependence: Associations with cortical thickness and N-acetylaspartate levels in the extended brain reward system. Addict. Biol. 18, 379-391.
- Durazzo, T.C., Mon, A., Pennington, D., Abe, C., Gazdzinski, S., Meyerhoff, D.J., 2014c. Interactive effects of chronic cigarette smoking and age on brain volumes in controls and alcohol-dependent individuals in early abstinence. Addict. Biol. 19, 132-143.
- Durazzo, T.C., Tosun, D., Buckley, S., Gazdzinski, S., Mon, A., Fryer, S.L., Meyerhoff, D.J., 2011b. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: Relationships to relapse and extended abstinence. Alcohol. Clin. Exp. Res. 35, 1187-1200.
- Eickhoff, S., Walters, N.B., Schleicher, A., Kril, J., Egan, G.F., Zilles, K., Watson, J.D., Amunts, K., 2005. High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. Hum. Brain Mapp. 24, 206-215.

- Fedota, J.R., Stein, E.A., 2015. Resting-state functional connectivity and nicotine addiction: Prospects for biomarker development. Ann. N.Y. Acad. Sci. 1349, 64-82.
- Fellows, L.K., Farah, M.J., 2005. Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. Cereb. Cortex. 15, 58-63.
- Fergusson, D.M., Goodwin, R.D., Horwood, L.J., 2003. Major depression and cigarette smoking: Results of a 21-year longitudinal study. Psychol. Med. 33, 1357-1367.
- Fettes, P., Schulze, L., Downar, J., 2017. Cortico-striatal-thalamic loop circuits of the orbitofrontal cortex: Promising therapeutic targets in psychiatric illness. Front. Syst. Neurosci. 11, 25.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1998. Structured clinical interview for DSM-IV Axis I Disorders - Patient edition (SCID-I/P, Version 2.0, 8/98 revision).Biometrics Research Department, New York, NY.
- Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U.S.A. 97, 11050-11055.
- Fischl, B., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A.M., 2004. Automatic parcellation of the human cerebral cortex. Cereb. Cortex. 14, 11-22.
- Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9, 195-207.
- Fjell, A.M., Grydeland, H., Krogsrud, S.K., Amlien, I., Rohani, D.A., Ferschmann, L., Storsve,A.B., Tamnes, C.K., Sala-Llonch, R., Due-Tonnessen, P., Bjornerud, A., Solsnes, A.E.,Haberg, A.K., Skranes, J., Bartsch, H., Chen, C.H., Thompson, W.K., Panizzon, M.S.,

Kremen, W.S., Dale, A.M., Walhovd, K.B., 2015. Development and aging of cortical thickness correspond to genetic organization patterns. Proc. Natl. Acad. Sci. U.S.A. 112, 15462-15467.

- Fjell, A.M., Walhovd, K.B., 2010. Structural brain changes in aging: Courses, causes and cognitive consequences. Rev. Neurosci. 21, 187-221.
- Fjell, A.M., Walhovd, K.B., Reinvang, I., Lundervold, A., Salat, D., Quinn, B.T., Fischl, B., Dale, A.M., 2006. Selective increase of cortical thickness in high-performing elderly— Structural indices of optimal cognitive aging. Neuroimage 29, 984-994.
- Froeliger, B., McConnell, P.A., Stankeviciute, N., McClure, E.A., Kalivas, P.W., Gray, K.M., 2015. The effects of N-Acetylcysteine on frontostriatal resting-state functional connectivity, withdrawal symptoms and smoking abstinence: A double-blind, placebocontrolled fMRI pilot study. Drug Alcohol Depend. 156, 234-242.
- Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega,
 B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., Grieve, S.M., Galatzer-Levy, I., Fox,
 P.T., Etkin, A., 2015. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72, 305-315.
- Grill-Spector, K., Weiner, K.S., 2014. The functional architecture of the ventral temporal cortex and its role in categorization. Nat. Rev. Neurosci. 15, 536-548.
- Hong, L.E., Gu, H., Yang, Y., Ross, T.J., Salmeron, B.J., Buchholz, B., Thaker, G.K., Stein,E.A., 2009. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. Arch. Gen. Psychiatry 66, 431-441.

- Karama, S., Ducharme, S., Corley, J., Chouinard-Decorte, F., Starr, J.M., Wardlaw, J.M., Bastin, M.E., Deary, I.J., 2015. Cigarette smoking and thinning of the brain's cortex. Mol. Psychiatry 20, 778-785.
- Kolb, B., Whishaw, I.Q., 2009. Fundamentals of human neuropsychology. Worth Publishers, New York, NY.
- Kremen, W.S., Prom-Wormley, E., Panizzon, M.S., Eyler, L.T., Fischl, B., Neale, M.C., Franz, C.E., Lyons, M.J., Pacheco, J., Perry, M.E., Stevens, A., Schmitt, J.E., Grant, M.D., Seidman, L.J., Thermenos, H.W., Tsuang, M.T., Eisen, S.A., Dale, A.M., Fennema-Notestine, C., 2010. Genetic and environmental influences on the size of specific brain regions in midlife: The VETSA MRI study. Neuroimage 49, 1213-1223.
- Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 72, 341-372.
- Kuhn, S., Schubert, F., Gallinat, J., 2010. Reduced thickness of medial orbitofrontal cortex in smokers. Biol. Psychiatry 68, 1061-1065.
- Li, S., Yang, Y., Hoffmann, E., Tyndale, R.F., Stein, E.A., 2017. CYP2A6 genetic variation alters striatal-cingulate circuits, network hubs, and executive processing in smokers. Biol. Psychiatry 81, 554-563.
- Li, Y., Yuan, K., Cai, C., Feng, D., Yin, J., Bi, Y., Shi, S., Yu, D., Jin, C., von Deneen, K.M.,
 Qin, W., Tian, J., 2015. Reduced frontal cortical thickness and increased caudate volume within fronto-striatal circuits in young adult smokers. Drug Alcohol Depend. 151, 211-219.

- McKee, S.A., Falba, T., O'Malley, S.S., Sindelar, J., O'Connor, P.G., 2007. Smoking status as a clinical indicator for alcohol misuse in US adults. Arch. Intern. Med. 167, 716-721.
- Mega, M.S., Cummings, J.L., 1994. Frontal-subcortical circuits and neuropsychiatric disorders.J. Neuropsychiatry Clin. Neurosci. 6, 358-370.
- Mertens, J.R., Weisner, C., Ray, G.T., Fireman, B., Walsh, K., 2005. Hazardous drinkers and drug users in HMO primary care: Prevalence, medical conditions, and costs. Alcohol. Clin. Exp. Res. 29, 989-998.
- Mon, A., Durazzo, T.C., Gazdzinski, S., Hutchison, K.E., Pennington, D., Meyerhoff, D.J., 2013. Brain-derived Neurotrophic Factor (BDNF) genotype is associated with lobar gray and white matter volume recovery in abstinent alcohol dependent individuals. Genes Brain Behav. 12, 98-107.
- Naqvi, N.H., Bechara, A., 2010. The insula and drug addiction: An interoceptive view of pleasure, urges, and decision-making. Brain Struct. Funct. 214, 435-450.
- Pan, P., Shi, H., Zhong, J., Xiao, P., Shen, Y., Wu, L., Song, Y., He, G., 2013. Chronic smoking and brain gray matter changes: Evidence from meta-analysis of voxel-based morphometry studies. Neurol. Sci. 34, 813-817.
- Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Jernigan, T.L., Prom-Wormley, E., Neale, M., Jacobson, K., Lyons, M.J., Grant, M.D., Franz, C.E., Xian, H., Tsuang, M., Fischl, B., Seidman, L., Dale, A., Kremen, W.S., 2009. Distinct genetic influences on cortical surface area and cortical thickness. Cereb. Cortex. 19, 2728-2735.
- Patton, J.H., Stanford, M.S., Barratt, E.S., 1995. Factor structure of the Barratt impulsiveness scale. J. Clin. Psychol. 51, 768-774.

- Paulus, M.P., 2007. Neural basis of reward and craving— A homeostatic point of view. Dialogues Clin. Neurosci. 9, 379-387.
- Peng, P., Li, M., Liu, H., Tian, Y.R., Chu, S.L., Van Halm-Lutterodt, N., Jing, B., Jiang, T., 2018. Brain structure alterations in respect to tobacco consumption and nicotine dependence: A comparative voxel-based morphometry study. Front. Neuroanat. 12, 43.

Rakic, P., 1988. Specification of cerebral cortical areas. Science 241, 170-176.

- Rakic, P., 2008. Confusing cortical columns. Proc. Natl. Acad. Sci. U.S.A. 105, 12099-12100.
- Richter, P., Werner, J., Heerlein, A., Kraus, A., Sauer, H., 1998. On the validity of the Beck Depression Inventory. A review. Psychopathology 31, 160-168.
- Rolls, E.T., Grabenhorst, F., 2008. The orbitofrontal cortex and beyond: From affect to decisionmaking. Prog. Neurobiol. 86, 216-244.
- Schilling, C., Kuhn, S., Paus, T., Romanowski, A., Banaschewski, T., Barbot, A., Barker, G.J.,
 Bruhl, R., Buchel, C., Conrod, P.J., Dalley, J.W., Flor, H., Ittermann, B., Ivanov, N.,
 Mann, K., Martinot, J.L., Nees, F., Rietschel, M., Robbins, T.W., Smolka, M.N., Strohle,
 A., Kathmann, N., Garavan, H., Heinz, A., Schumann, G., Gallinat, J., 2013. Cortical
 thickness of superior frontal cortex predicts impulsiveness and perceptual reasoning in
 adolescence. Mol. Psychiatry 18, 624-630.
- Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349-2356.
- Sharma, A., Brody, A., 2009. In vivo brain imaging of human exposure to nicotine and tobacco. Handb. Exp. Pharmacol. 192, 145-171.

- Skinner, H.A., Sheu, W.J., 1982. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. J. Stud. Alcohol 43, 1157-1170.
- Sobell, L.C., Sobell, M.B., Riley, D.M., Schuller, R., Pavan, D.S., Cancilla, A., Klajner, F., Leo,G.I., 1988. The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past. J. Stud. Alcohol 49, 225-232.
- Spielberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A., 1977. Self-evaluation questionnaire. Consulting Psychologist Press, Palo Alto, CA.
- Storsve, A.B., Fjell, A.M., Tamnes, C.K., Westlye, L.T., Overbye, K., Aasland, H.W., Walhovd, K.B., 2014. Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: Regions of accelerating and decelerating change. J. Neurosci. 34, 8488-8498.
- Sutherland, M.T., Carroll, A.J., Salmeron, B.J., Ross, T.J., Hong, L.E., Stein, E.A., 2013. Downregulation of amygdala and insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. Biol. Psychiatry 74, 538-546.
- Sutherland, M.T., Riedel, M.C., Flannery, J.S., Yanes, J.A., Fox, P.T., Stein, E.A., Laird, A.R.,
 2016. Chronic cigarette smoking is linked with structural alterations in brain regions showing acute nicotinic drug-induced functional modulations. Behav. Brain Funct. 12, 16.
- Sweitzer, M.M., Geier, C.F., Addicott, M.A., Denlinger, R., Raiff, B.R., Dallery, J., McClernon,
 F.J., Donny, E.C., 2016. Smoking abstinence-induced changes in resting state functional connectivity with ventral striatum predict lapse during a quit attempt. Neuropsychopharmacology 41, 2521-2529.

- Vemuri, P., Wiste, H.J., Weigand, S.D., Knopman, D.S., Trojanowski, J.Q., Shaw, L.M., Bernstein, M.A., Aisen, P.S., Weiner, M., Petersen, R.C., Jack, C.R., Jr., 2010. Serial MRI and CSF biomarkers in normal aging, MCI, and AD. Neurology 75, 143-151.
- Walhovd, K.B., Fjell, A.M., Dale, A.M., Fischl, B., Quinn, B.T., Makris, N., Salat, D., Reinvang,I., 2006. Regional cortical thickness matters in recall after months more than minutes.Neuroimage 31, 1343-1351.
- WHO, 2015. WHO global report on trends in prevalence of tobacco smoking 2015. World Health Organization, Geneva.
- Williams, L.M., 2016. Precision psychiatry: A neural circuit taxonomy for depression and anxiety. Lancet Psychiatry 3, 472-480.
- Winkler, A.M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P.T., Duggirala, R., Glahn, D.C., 2010. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage 53, 1135-1146.

Figure Legends

Figure 1. ESER Regions significantly different between Non-Smokers and Smokers.

- Figure 2. AD Regions significantly different between Non-Smokers and Smokers.
- Figure 3. Association of middle temporal gyri thickness and pack years in Smokers.
- Figure 4. Association of IGT Net Total Score and superior frontal gyri thickness in Smokers.

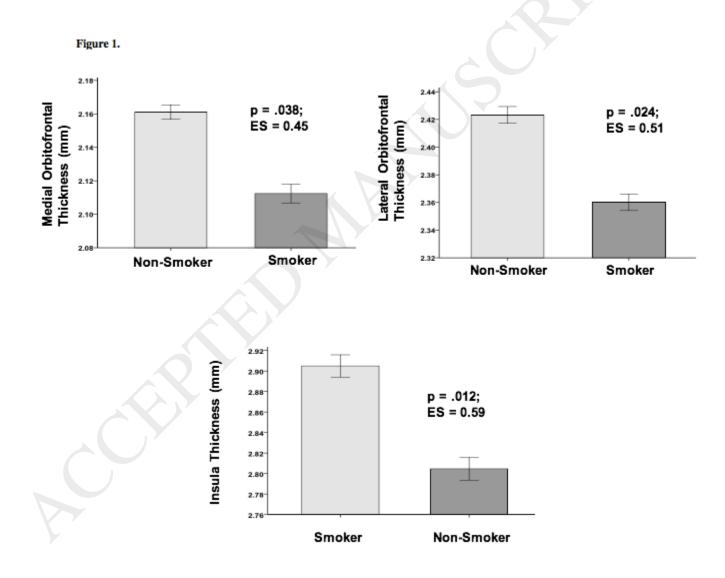
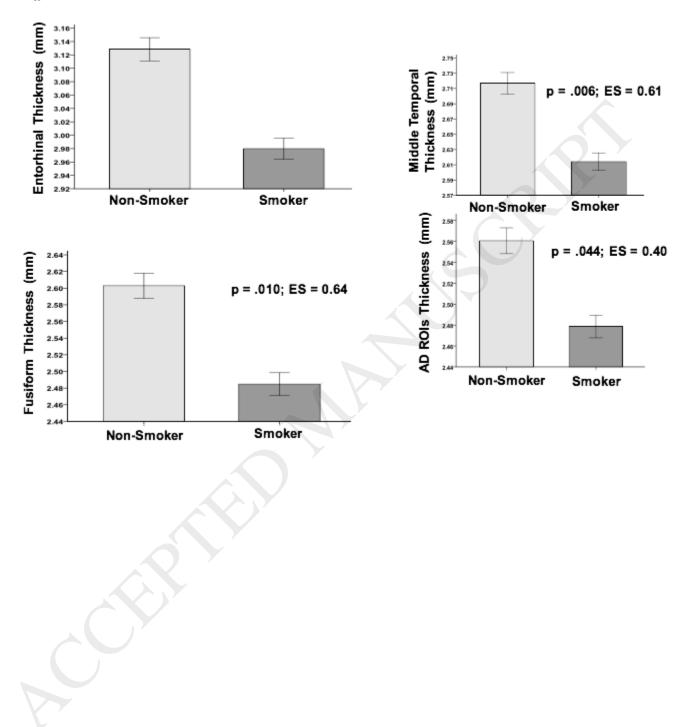
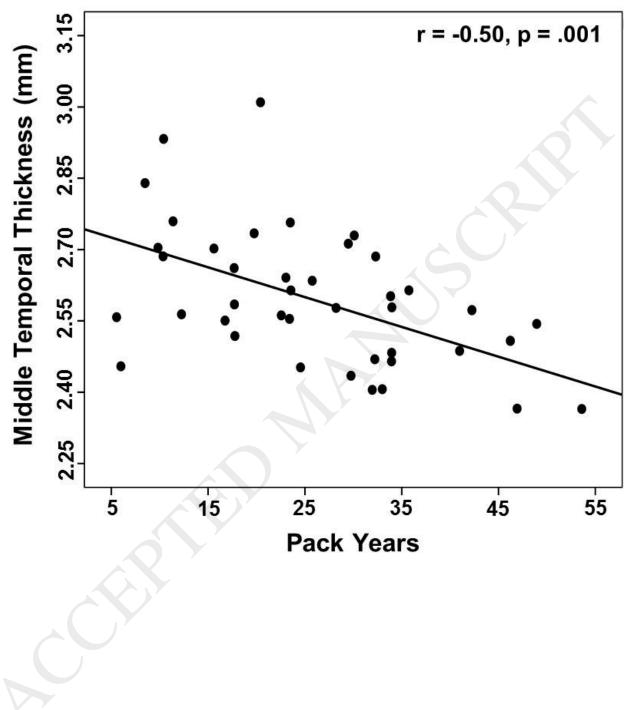
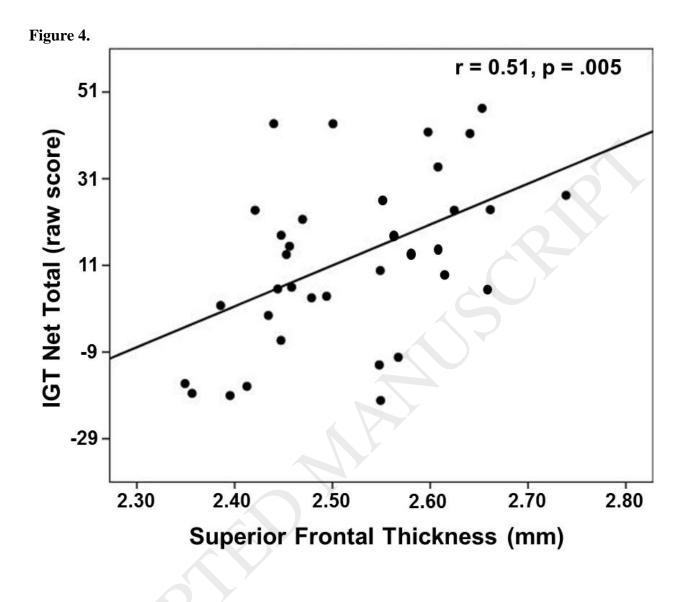


Figure 2.









_ Measure	Non-smokers	Smokers
	(n = 41)	(n = 41)
_		
Age (years)	43.2 (12.3)	46.6 (11.0)
Education (years)	16.1 (2.2)	14.8 (2.0)*
Male (%)	83	85
Caucasian (%)	56	68
Lifetime average		
drinks/month	18 (11) 26 (14	4)*
FTND	NA	5 (2)
Pack-years	NA	25 (13)
BDI	3 (3)	6 (4)*
STAI	32 (7)	34 (9)
Intracranial volume (cc)	1413 (203)	1425 (249)

Table 1. Group Demographics, Alcohol and Cigarette Use Histories, and Self-Report Questionnaires

Note. BDI: Beck Depression Inventory. CON: Controls. FTND: Fagerstrom Tolerance Test for Nicotine Dependence. NA: not applicable. STAI: State -trait Anxiety Inventory – Trait. *Smokers > Non-smokers, p < .05. Mean (SD).