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Greater regional brain atrophy rate in healthy elders with a history of cigarette smoking

Timothy C. Durazzo, PhD[a,b,*], **Philip S. Insel, MS**[a], **Michael W. Weiner, MD**[a,b,c], and **the Alzheimer Disease Neuroimaging Initiative**[#]

[a]Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco VA Medical Center, San Francisco, CA, USA

[b]Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

[c]Departments of Psychiatry, Medicine, and Neurology, University of California, San Francisco Psychiatry, University of California, San Francisco, CA, USA

Abstract

Background—Little is known about the effects of cigarette smoking on brain morphological changes in the elderly. This study investigated the effects of a history of cigarette smoking on changes in regional brain volumes over 2-years in healthy, cognitively-intact elderly individuals. We predicted individuals with a history of cigarette smoking, compared to never smokers, demonstrate greater rate of atrophy over 2-years in regions that manifest morphological abnormalities in the early stages of Alzheimer Disease (AD), as well as the extended brain reward system (BRS), which is implicated in the development and maintenance of substance use disorders.

Methods—Participants were healthy, cognitively normal elderly controls (75.9±4.8 years of age) with any lifetime history of cigarette smoking (n = 68) and no history of smoking (n = 118). Data was obtained via the Alzheimer Disease Neuroimaging Initiative from 2005–2010. Participants completed four magnetic resonance scans over 2-years. A standardized protocol employing high resolution 3D T_1-weighted sequences at 1.5 Tesla was used for structural imaging and regional brain volumetric analyses.

Results—Smokers demonstrated significantly greater rate atrophy over 2-years than non-smokers in multiple brain regions associated with the early stages of AD as well as in the BRS. Groups were not different on rate of global cortical atrophy.

Conclusions—A history of cigarette smoking in this healthy elderly cohort was associated with decreased structural integrity of multiple brain regions, which was manifest as a greater rate of atrophy over 2-years in regions specifically affected by incipient AD as well as chronic substance abuse.

[*]Author to whom correspondence should be addressed: Center for Imaging of Neurodegenerative Diseases (114M) San Francisco VA Medical Center 4150 Clement Street San Francisco, CA 94121, USA timothy.durazzo@ucsf.edu.

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Keywords

Alzheimer Disease; MRI, neuroimaging; brain volumes; brain reward system; substance abuse; nicotine; brain atrophy; longitudinal

1. Introduction

The general health consequences associated with chronic cigarette smoking are well documented[1]. However, little research has been specifically devoted to the effects of smoking on human neurobiology over time[2]. Early computed tomography (CT) studies demonstrated that chronic cigarette smoking was associated with increases of global brain atrophy with advancing age[3-6]. More recent cross-sectional magnetic resonance imaging (MRI) studies revealed that chronic cigarette smoking in non-demented middle-aged and elderly adults was independently associated with regionally specific abnormalities in brain morphology and biochemistry. Specifically, smokers demonstrated smaller gray matter (GM) volumes and/or lower GM densities than non-smokers in the anterior cingulate, dorsolateral and orbitofrontal cortex, parahippocampal gyrus and precuneus, smaller volumes in the left dorsal ACC and lower gray matter densities in the right cerebellum[7-10]. Chronic smokers demonstrated lower cortical thickness medial orbitofrontal cortex[39] and lower N-acetylaspartate concentration (a surrogate marker of neuronal integrity [11, 12]) in the left hippocampus relative to non-smokers[13].

Taken together, previous neuroimaging studies suggest that chronic cigarette smoking is associated with neurobiological abnormalities in regions that also exhibit morphological abnormalities in the incipient stages of Alzheimer disease[14] (AD) (e.g., hippocampus, entorhinal cortex, parahippocampal gyrus, posterior cingulate region) as well as morphological abnormalities in components of the extended brain reward system (BRS) in observed in substance use disorders[15]. Neurobiological abnormalities in the BRS are implicated as major contributors to the development and persistence of all forms of addiction, including nicotine dependence[16]. Cortical components of the BRS include the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), insula, anterior cingulate cortex (ACC) as well as the amygdala, hippocampus and other regions/nuclei in the dorsal and ventral striatum and basal forebrain[17-19].

To date, no study has specifically investigated the longitudinal effects of a history of cigarette smoking on brain volumes in regions that manifest abnormalities in the early stages of AD or in the BRS in elderly adults free of clinically significant cardiovascular, cerebrovascular and neurodegenerative diseases. Consequently, it is unknown if a history of cigarette smoking is associated with regionally specific volume changes in healthy elderly individuals over time. The primary objective of this study was to compare volume changes in elderly individuals with a history of cigarette smoking (smokers) to those with no history of smoking over lifetime (non-smokers) over a 2-year period with serial high resolution MRI. We focused on regions that demonstrate morphological abnormalities during the incipient stages of AD as well as in BRS regions that show morphological changes in those with substance use disorders. We predicted smokers, compared to non-smokers, demonstrate significantly greater rate of atrophy over 2-years in 1) regions associated with morphological abnormalities in the early stages of AD including the hippocampus, entorhinal cortex, parahippocampal gyrus, posterior cingulate region (posterior cingulate gyrus and isthmus), precuneus and fusiform gyrus, and 2) in components of the BRS including the ACC (rostral and caudal divisions), DLPFC (inferior frontal gyri, rostral and caudal middle frontal gyri, superior frontal gyri) insula, orbitofrontal region (medial and lateral regions, pars orbitalis) and amygdala.

2. Methods

2.1. Participants

The cohort examined consisted of a sub-sample of 186 participants (75.9 ± 4.8 years of age at baseline examination) who served as controls in the Alzheimer Disease Neuroimaging Initiative (ADNI) project. The following is a standard description of the ADNI project (see http://adni.loni.ucla.edu/about/): "ADNI is a multisite study supported by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a 5-year public-private partnership[20, 21]. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The initial goal of ADNI was to recruit 800 adults from approximately 58 sites in the United States and Canada, ages 55 to 90, to participate in the research –approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years." Participants in this study were recruited from multiple sites in the United States from 2005 – 2010. Written informed consent was obtained from all participants before initiation of procedures. The study was conducted according to the Declaration of Helsinki, and U.S. 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards [45, 46]. Participants who reported no tobacco use during lifetime were assigned to the non-smoker (n = 118) group; those who reported any history of cigarette smoking during lifetime were designated as smokers (n = 68). Three of the smokers also smoked pipes or cigars. Basic information regarding duration of smoking over lifetime and duration of abstinence from cigarettes was available for 58 smokers. At the time of the baseline study, 7.4 percent of the smokers were actively smoking. See Table 1 for demographic information on smokers and non-smokers.

2.2. MRI image acquisition and processing

2.2.1. Acquisition—Participants completed four MR scanning sessions (discounting missed visits and subjects who had not yet reached 2 years) at baseline and 6, 12 and 24 months after baseline at multiple ADNI sites. A standardized protocol employed high resolution 3D T_1-weighted sequences acquired at both 1.5 and 3 Tesla (T) for morphometric analyses[22]. Since the majority of participants were scanned at 1.5T, analyses were confined to 1.5T data to avoid the potential confounding effect of scanner field strength on tissue volume quantification. In each of the four 1.5T scanning sessions, participants completed a T1-weighted (3D sagittal volumetric magnetization prepared rapid gradient echo sequence) and a 3D T2-weighted scan sequences. Acquisition parameters are fully described elsewhere[22]. All images were calibrated with phantom-based geometric corrections to ensure consistency among scans across different sites[23].

2.2.2. Processing—The publically available Freesurfer (version 4.4) volumetric segmentation and cortical surface reconstruction methods[24-27] were used to obtain regional measures of regional cortical and subcortical volumes (mm^3). A normalized intensity image was created after correction for field inhomogeneities and the skull and other extrinsic, non-parenchymal tissue had been removed. The intensity normalized, skull-stripped image was then further processed by a segmentation procedure based on the geometric structure of the gray–white interface. The resulting volume was covered with a triangular tessellation and deformed to produce an accurate and smooth representation of the gray/white interface and

pial surface. Vertex-based cortical thickness measurements were obtained as the distance between the reconstructed surface representations of the gray-white interface and pial surfaces. The reconstructed cortical surface models for each participant were manually inspected to ensure segmentation accuracy. Each cortical surface was spatially normalized to a template cortical surface using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns. Spatial normalization to the template surface allowed automatic parcellation of the cortical surface for each participant into 34 anatomical regions per hemisphere. Subcortical segmentation of the amygdala, hippocampus, caudate, putamen, nucleus accumbens and cerebellum was also completed. An average bilateral volume was calculated for all cortical and subcortical ROIs. A global GM volume was obtained by calculating the average of all cortical and subcortical ROIs and GM nuclei. White matter hyperintensity volume was derived from T2-weighed images.

2.3. Statistical analyses

2.3.1. Baseline—Smokers and non-smokers were compared on regional baseline volumes, demographic, biomedical, psychiatric and behavioral variables (see Table 1) with the Kruskal-Wallis Test and Fisher's Exact Test where appropriate[28]. Analyses comparing baseline regional volumes among smokers and non-smokers analyses were adjusted for the following baseline variables to control for their potential mediating effects on brain volume: age, gender, intracranial volume, total white matter hyperintensity volume, BMI, respiratory symptoms, plasma homocysteine ADAS-cog score (a measure of global cognitive level, functioning), and geriatric depression inventory score. In the smoker group, duration of smoking over lifetime and duration of smoking cessation were related to baseline AD and BRS ROIs. A false discovery rate (FDR) correction[29] adjusted p-values for multiplicity of tests in all analyses and a FDR corrected alpha level $p \leq .05$ was considered statistically significant.

2.3.2 Longitudinal—Assessment of changes group in regional brain volumes across the 2-year interval was conducted with linear mixed-effects models[30]. Two separate analyses were performed. Longitudinal analysis 1 the volume trajectory in smokers and non-smokers was compared on the 8 AD regions and 10 BRS regions specified *a priori* to show greater rate of atrophy in smokers versus non-smokers. In longitudinal analysis 2, the volume trajectory in smokers and non-smokers was compared over all 34 parcellated cortical regions, segmented subcortical regions, and global cortical GM volume. The objective of analysis 2 was to determine if smokers showed a differential atrophy rate in regions outside the defined AD and BRS ROIs as well as for global cortical GM volume. Factors in both longitudinal analyses were group (smoker, non-smoker), age, gender, intracranial volume, total white matter hyperintensity volume, BMI, respiratory symptoms, plasma homocysteine level, ADAS-cog score, and geriatric depression inventory score. In both longitudinal analyses, random intercepts and slopes were estimated and an auto-regressive covariance structure was applied. FDR correction adjusted p-values for multiplicity of tests in both longitudinal analysis 1 and 2, and a corrected alpha level $p \leq .05$ was considered statistically significant. Additionally, in the smoker group, duration of smoking over lifetime and duration of smoking cessation was related to volume change in AD and BRS ROIs. FDR correction adjusted p-values for multiplicity of tests. The effect of attrition was evaluated by regression of a missing indicator for volumetric data at month 24 on smoking status and other covariates. All cross-sectional analyses and longitudinal were completed with R (v2.10.1).

3. Results

3.1. Baseline volumes, demographic, biomedical, psychiatric and behavioral variables

Groups were not significantly different on demographic, biomedical, psychiatric, behavioral variables except for higher BMI in smokers ($p = .01$) and a trend ($p = .07$) for higher frequency of self-reported respiratory symptoms in smokers (see Table 1). No significant baseline volume differences were observed between smokers and non-smokers in any individual ROI, global cortical volume or on total white matter hyperintensity volume. In smokers, longer smoking duration over lifetime was related to smaller baseline superior frontal gyrus volume ($r = -0.43$, $p = .036$). There were no associations between AD and BRS ROIs and duration of abstinence from cigarettes. Twenty-six non-smokers (22%) and 16 smokers (23.5%) did not have MRI data at the 2-year assessment point. There were no significant differences in baseline demographic and clinical measures of participants who completed versus those who did not complete the 2-year assessment point. Additionally, smoking status was not associated with dropout over the 2-year assessment interval ($p=0.94$). Taken together, this indicates and there was no ostensible influence of demographic and clinical variables or smoking status on participant attrition.

3.2. Longitudinal volumes

In longitudinal analysis 1, significant group x time interactions were apparent in the majority of specified AD and BRS ROIs (see Table 2), with a trend for the superior frontal gyrus ($p = 0.07$), where smokers demonstrated a significantly greater rate of atrophy than non-smokers over the 2-year assessment interval. These findings largely support our *a priori* predictions. In longitudinal analysis 2, where all 34 cortical and 8 subcortical ROIs were simultaneously compared, significant group x time interactions were also observed for the frontal pole, middle temporal gyrus, inferior parietal lobule and lingual gyrus, where smokers demonstrated a significantly greater rate of atrophy than non-smokers. For all ROIs demonstrating a group x time interactions there was a significant effect for time indicating volume loss for both groups across the assessment interval, but, as indicated by the interactions, the rate of atrophy was significantly greater in smokers. Smokers and non-smokers were not significantly different on any individual ROI or global brain volume at 6, 12 or 24 months. In smokers, longer smoking duration over lifetime was related to greater volume loss in the superior frontal gyrus over the 2-year assessment interval ($p = .035$) with a trend for the caudal middle frontal gyrus ($p = .06$).

4. Discussion

The major findings of this study were: 1) healthy elders with a history of cigarette smoking demonstrated significantly greater rates of volume loss over 2-years than lifetime non-smokers in posterior neocortical and paralimbic brain regions associated with morphological abnormalities in AD, specifically, in the posterior cingulate region, inferior parietal lobule, parahippocampal gyrus, fusiform gyrus, lingual gyrus, precuneus and middle temporal gyrus; 2) elders with a smoking history also demonstrated greater longitudinal volume loss compared to lifetime non-smokers in anterior frontal regions involving major cortical components of the BRS, specifically, in the orbitofrontal cortex, frontal pole, pars orbitalis, pars triangularis, rostral middle frontal gyrus. Smokers did not show a greater rate of atrophy in subcortical regions or for the global cortex relative to non-smokers. The greater regional cortical atrophy in smokers was not mediated by age, sex and other potentially confounding factors; 3) smoking duration over lifetime was only related to baseline volume and volume change in the superior frontal gyrus.

The identification of greater longitudinal atrophy rates in healthy elderly individuals with a history of smoking in specific anterior frontal and posterior cortical regions represent a significant extension of the findings from previous neuroimaging studies. The cortical AD and BRS regions that showed significantly greater atrophy rates in smokers collectively account for approximately 38% of the total cortex, however, smokers and non-smokers did not differ in the rate of global cortical atrophy. Overall, the findings suggest a history of cigarette smoking in this cohort was associated a greater rate of tissue loss rate in two localized and spatially distinct cortical regions, rather than with an increased rate of generalized atrophy across the cortex and subcortical nuclei/regions. The regions that showed greater rates of atrophy in smokers are consistent with previous cross-sectional neuroimaging studies that observed significant regional morphological and biochemical abnormalities (e.g., dorsolateral prefrontal, orbitofrontal, posterior cingulate, parahippocampal regions) in smokers[6-9]. Contrary to previous cross-sectional studies, smokers and non-smokers in this study did not differ on regional baseline volumes or global cortical volume. The equivalence of groups on regional baseline volumes highlights the importance and power of serial longitudinal MR assessment to track relevant structural brain changes over time in conditions and diseases that are associated with compromised brain morphology [31].

The AD neocortical and paralimbic regions that demonstrated greater atrophy rates in smokers in this study are involved in learning, memory and processing of complex visual social and emotional cues[32]. The anterior frontal neocortical BRS regions that showed greater atrophy rates in smokers subserve complex problem-solving, abstract reasoning, working memory, shifting or maintaining behavior according to environmental contingencies and modifying reward-and-punishment-related behavior[33, 34]. As such, neurobiological abnormalities in the BRS are implicated in the development and maintenance of all forms of addictive disorders, including nicotine dependence[1, 16]. If the greater atrophy rate observed in smokers across the AD and BRS regions measured in this study progresses at a similar magnitude over time, these participants may be at increased risk for neurocognitive dysfunction[35]. Furthermore, irrespective of the potential mechanism, a history of chronic smoking is strongly linked to significantly increased risk for development of AD[36-38].

There are several potential mechanisms that may contribute independently, or in concert, to the significantly greater regionally specific atrophy rates observed in smokers. Chronic cigarette smoking is associated with increased risk for numerous biomedical conditions including cardiovascular and cerebrovascular disease[39-42] that may directly or indirectly compromise brain neurobiology. Nicotine is but one of more than 4000 compounds composing the particulate and gas phases of cigarette smoke. The many potentially cytotoxic compounds in cigarette smoke (e.g., carbon monoxide, aldehydes, nitrosamines, dihydroxybenzenes) may directly compromise neuronal and cellular membrane function of cerebral tissue. Specifically, cigarette smoke provides a continued sustained direct source of exogenous free radical species, carbon monoxide and other potentially cytotoxic compounds[1,43, 44]. Duration of smoking over lifetime and duration of abstinence from cigarettes were not associated with volumes in multiple ROIs in smokers (after correcting for multiple comparisons); however, chronic exposure to these noxious agents, in combination with potential sub-clinical cardiopulmonary and/or cerebrovascular disease, may have created vulnerability for increased cortical brain atrophy rates or exacerbated a pre-existing susceptibility for greater volume loss during senescence in the smoking group. Additionally, the rate of regional atrophy demonstrated by smokers may have been diminished by a survivor effect [37], given the age range of participants in this study.

This study has limitations that may affect the generalizability of the findings. Comprehensive information on smoking history was not obtained; therefore, pack years could not be calculated for most smoking participants. The vast majority of smokers were not current smokers and the available information on tobacco use demonstrated considerable heterogeneity with respect to duration of regular tobacco use and last use. Unrecorded group differences in nutrition, exercise, overall physical health, exposure to environmental cigarette smoke or genetic predispositions (other than *APOE ε4* genotype) may also have contributed to the greater regional atrophy rates demonstrated by smoking history.

In conclusion, this serial longitudinal assessment demonstrated that a history of cigarette smoking in healthy non-demented elderly individuals was associated with a significantly greater rate of atrophy over a 2-year period in posterior cortical regions that show morphological abnormalities in the early stages of AD as well as in anterior cortical regions implicated in the development and maintenance of substance use disorders. Additional research is necessary to indentify the potential mechanisms associated with the greater atrophy rate observed in those with a history of cigarette smoking, and to assess if participants with a history of smoking continue to demonstrate a greater rate of atrophy beyond the 2-year interval assessed in this study. Further study is needed to assess the neurocognitive and functional consequences of the greater rate of atrophy demonstrated by the smoking cohort and to investigate if smoking in this cohort is associated with greater risk of developing mild cognitive impairment.

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6. References

1. Durazzo TC, Meyerhoff DJ. Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. Front Biosci. 2007; 12:4079–100. [PubMed: 17485360]
2. Durazzo TC, Meyerhoff DJ, Nixon SJ. Chronic cigarette smoking: implications for neurocognition and brain neurobiology. Int J Environ Res Public Health. 2010; 7(10):3760–91. [PubMed: 21139859]
3. Akiyama H, Meyer JS, Mortel KF, Terayama Y, Thornby J, Konno S. Normal human aging: factors contributing to cerebral atrophy. Journal of Neurological Sciences. 1997; 152:39–49.
4. Hayee A, Haque A, Anwarullah A, Rabbani M. Smoking enhances age related brain atrophy-a quantitative study with computed tomography. Bangladesh Med Res Counc Bull. 2003; 29(3):118–24. [PubMed: 15053274]
5. Kubota K, Matsuzawa T, Fujiwara T, et al. Age-related brain atrophy enhanced by smoking: a quantitative study with computed tomography. J exp Med. 1987; 153:303–11.

6. Longstreth WT Jr. Arnold AM, Manolio TA, et al. Clinical correlates of ventricular and sulcal size on cranial magnetic resonance imaging of 3,301 elderly people. The Cardiovascular Health Study. Collaborative Research Group. Neuroepidemiology. 2000; 19(1):30–42. [PubMed: 10654286]
7. Brody AL, Mandelkern MA, Jarvik ME, et al. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol Psychiatry. 2004; 55(1):77–84. [PubMed: 14706428]
8. Gallinat J, Meisenzahl E, Jacobsen LK, et al. Smoking and structural brain deficits: a volumetric MR investigation. Eur J Neurosci. 2006; 24(6):1744–50. [PubMed: 17004938]
9. Zhang X, Salmeron BJ, Ross TJ, Geng X, Yang Y, Stein EA. Factors underlying prefrontal and insula structural alterations in smokers. Neuroimage. 2011; 54(1):42–8. [PubMed: 20699124]
10. Almeida OP, Garrido GJ, Lautenschlager NT, Hulse GK, Jamrozik K, Flicker L. Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. Am J Geriatr Psychiatry. 2008; 16(1):92–8. [PubMed: 18165464]
11. Ross B, Bluml S. Magnetic resonance spectroscopy of the human brain. Anat Rec. 2001; 265(2): 54–84. [PubMed: 11323770]
12. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM. N-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. Prog Neurobiol. 2007; 81(2):89–131. [PubMed: 17275978]
13. Gallinat J, Lang UE, Jacobsen LK, et al. Abnormal hippocampal neurochemistry in smokers: evidence from proton magnetic resonance spectroscopy at 3 T. J Clin Psychopharmacol. 2007; 27(1):80–4. [PubMed: 17224719]
14. Krueger CE, Dean DL, Rosen HJ, et al. Longitudinal Rates of Lobar Atrophy in Frontotemporal Dementia, Semantic Dementia, and Alzheimer's Disease. Alzheimer Dis Assoc Disord. 2010; 24(1):43–8. [PubMed: 19571735]
15. Fowler JS, Volkow ND, Kassed CA, Chang L. Imaging the addicted human brain. Sci Pract Perspect. 2007; 3(2):4–16. [PubMed: 17514067]
16. Baler RD, Volkow ND. Drug addiction: the neurobiology of disrupted self-control. Trends Mol Med. 2006; 12(12):559–66. [PubMed: 17070107]
17. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry. 2005; 162(8):1403–13. [PubMed: 16055761]
18. Makris N, Oscar-Berman M, Jaffin SK, et al. Decreased volume of the brain reward system in alcoholism. Biol Psychiatry. 2008; 64(3):192–202. [PubMed: 18374900]
19. Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos Trans R Soc Lond B Biol Sci. 2008; 363(1507): 3191–200. [PubMed: 18640912]
20. Mueller SG, Weiner MW, Thal LJ, et al. The Alzheimer's disease neuroimaging initiative. Neuroimaging clinics of North America. 2005; 15(4):869–77, xi-xii. [PubMed: 16443497]
21. Mueller SG, Weiner MW, Thal LJ, et al. Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement. 2005; 1(1):55–66. [PubMed: 17476317]
22. Jack CR Jr. Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging. 2008; 27(4):685–91. [PubMed: 18302232]
23. Gunter JL, Bernstein MA, Borowski B, Felmlee JP, Blezek D, Mallozzi R. Validation testing of the MRI calibration phantom for the Alzheimer's disease neuroimaging initiative study. ISMRM 14th Scientific Meeting and Exhibition. 2006
24. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 1999; 9(2):179–94. [PubMed: 9931268]
25. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 1999; 9(2):195–207. [PubMed: 9931269]
26. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 2000; 97(20):11050–5. [PubMed: 10984517]
27. Fischl B, Destrieux C, Halgren E, et al. Automatic parcellation of the human cerebral cortex. Cereb Cortex. 2004; 14(1):11–22. [PubMed: 14654453]

28. Judd, CM.; McClelland, GH. Data Analysis: A Model-Comparison Approach. Harcourt Brace Jovanovich; San Diego, CA: 1989.
29. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society. 1995; 57:289–300. (Series B).
30. Pinheiro, J.; Bates, D. Mixed-Effects Models in S and S-PLUS. Springer-Verlag; New York: 2000.
31. Schuff N, Woerner N, Boreta L, et al. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. Brain. 2009; 132(Pt 4):1067–77. [PubMed: 19251758]
32. Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron. 2004; 44(1):195–208. [PubMed: 15450170]
33. Mega MS, Cummings JL. Frontal-subcortical circuits and neuropsychiatric disorders. J Neuropsychiatry Clin Neurosci. 1994; 6(4):358–70. [PubMed: 7841807]
34. Rolls ET, Grabenhorst F. The orbitofrontal cortex and beyond: from affect to decision-making. Prog Neurobiol. 2008; 86(3):216–44. [PubMed: 18824074]
35. Cardenas VA, Chao LL, Studholme C, et al. Brain atrophy associated with baseline and longitudinal measures of cognition. Neurobiol Aging. 2009
36. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. AmJEpidemiol. 2007; 166(4):367–78.
37. Cataldo JK, Glantz SA. Smoking cessation and Alzheimer's disease: facts, fallacies and promise. Expert Rev Neurother. 2010; 10(5):629–31. [PubMed: 20420482]
38. Rusanen M, Kivipelto M, Quesenberry CP Jr. Zhou J, Whitmer RA. Heavy Smoking in Midlife and Long-term Risk of Alzheimer Disease and Vascular Dementia. Arch Intern Med. 2010
39. Bolego C, Poli A, Paoletti R. Smoking and gender. Cardiovasc Res. 2002; 53(3):568–76. [PubMed: 11861027]
40. Garey KW, Neuhauser MM, Robbins RA, Danziger LH, Rubinstein I. Markers of inflammation in exhaled breath condensate of young healthy smokers. Chest. 2004; 125(1):22–6. [PubMed: 14718416]
41. Hawkins BT, Brown RC, Davis TP. Smoking and ischemic stroke: a role for nicotine. Trends in Pharmacological Sciences. 2002; 23(2):78–82. [PubMed: 11830264]
42. Tsushima Y, Tanizaki Y, Aoki J, Endo K. MR detection of microhemorrhages in neurologically healthy adults. Neuroradiology. 2002; 44(1):31–6. [PubMed: 11942497]
43. Bates, C.; Jarvis, M.; Connolly, G. Tobacco Additives: Cigarette engineering and nicotine addiction. July. Vol. 14. Massachusetts Tobacco Control Program; Boston: 1999. p. 1999
44. Fowles, J.; Bates, M.; Noiton, D. The Chemical Constituents in Cigarettes and Cigarette Smoke: Priorities for Harm Reduction. Epidemiology and Toxicology Group; New Zealand: Mar. 2000
45. Goodyear MDE, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki". BMJ. 2007; 335:624–5. [PubMed: 17901471]
46. U.S. Food and Drug Administration. Code of Federal Regulations, Title 21. 1 CITE: 21CFR50. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=50&showfr=1.

Table 1

Group baseline demographic, biomedical, psychiatric, behavioral measures

Variable	Non-smokers (n = 118)	Smokers (n = 68)
Age	76.6 (5.2)	75.2 (4.5)
Males %[#]	49	56
Education	16.3 (2.9)	15.7 (2.7)
Caucasian %[#]	91	94
APOE ε4 carrier %[#]	29.7	25.0
Current smokers%	NA	7.4
White matter lesion volume (cc)	8.4 (0.65)	8.3 (0.62)
Body Mass Index	26.6 (4.0)	28.6 (5.1)[*]
Modified Hachinski Score	0.70 (0.80)	0.61 (0.71)
Homocystine level (plasma)	9.8 (2.7)	10.4 (3.0)
GGT level (plasma)	23.5 (13.1)	23.3 (15.7)
Triglycerides (plasma)	136.8 (82.0)	156.8 (97.2)
Cholesterol (plasma)	194.0 (38.4)	194.4 (45.4)
Cardiovascular symptoms %	66	68
Respiratory symptoms %	19	27
Neurologic symptoms %	20	19
Hepatic symptoms %	1	5
Gastrointestinal symptoms %	43	52
Psychiatric symptoms %	19	27
Geriatric Depression Inventory	0.7 (1.1)	1.0 (1.2)
ADAS-cog score	6.0 (3.0)	6.0 (2.8)

Note.

all other comparisons between smokers and non-smokers conducted with the Kruskal-Wallis Test; GGT: gamma; glutamyltransferase; NA: not applicable.

[*] $p < .05$

[#] Fisher's Exact Test

Table 2

Annualized atrophy rate differences for smokers and nonsmokers in statistically significant regions of interest

Region	Rate Difference (mm^3/year)	Standard error	Corrected p-value
BRS/Anterior Brain Regions			
Rostral Middle frontal gyrus	-201.73	70.24	0.02
Pars triangularis	-51.54	17.38	0.02
Medial Orbitofrontal Cortex	-56.22	22.05	0.03
Pars Orbitalis	-28.49	10.77	0.03
Lateral Orbitofrontal Cortex	-66.30	29.08	0.04
Frontal Pole	-17.24	6.24	0.04
AD/Posterior Brain Regions			
Isthmus of Cingulate gyrus	-28.76	9.94	0.02
Inferior parietal lobule	-193.24	64.87	0.02
Posterior Cingulate Gyrus	-42.55	15.75	0.03
Precuneus	-108.96	40.79	0.03
Lingual Gyrus	-61.00	24.61	0.03
Parahippocampal Gyrus	-25.00	10.95	0.04
Fusiform Gyrus	-91.62	39.54	0.04
Middle Temporal Gyrus	-120.61	46.91	0.04

Note. Rate difference for each region indicates the amount of tissue volume lost per year in smokers relative to non-smokers. AD: Alzheimer Disease; BRS: Brain Reward System.