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A Comprehensive Assessment of Neurocognition in Middle-Aged Chronic Cigarette Smokers

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Abstract

Background—The majority of studies investigating the neurocognitive consequences of chronic smoking have been conducted with adults 60 years and older. Therefore, the scope of neurocognitive dysfunction associated with chronic cigarette smoking in middle age (i.e., 30–60 age range) has not been fully delineated.

Methods—Twenty-seven (44±9 years of age; 4 females) non-smoking and 30 smoking (49±8 years of age; 4 females) participants completed a comprehensive neurocognitive battery and measures of fine motor dexterity and postural stability. All participants were free of biomedical or psychiatric conditions that may have influenced neurocognitive and motor function.

Results—Smokers performed significantly worse than non-smokers on the following domains: auditory-verbal and visuospatial learning, visuospatial memory, cognitive efficiency, executive skills, general intelligence, processing speed, fine motor dexterity and postural stability. The differences between smokers and non-smokers evidenced moderate to strong effect sizes and were not mediated by age, education, vocational level, estimated verbal intelligence or alcohol consumption. In smokers, a greater number of lifetime years of smoking was related to poorer performance on measures of cognitive efficiency, processing speed and visuospatial skills.

Conclusions—Results from this middle-aged cohort replicated previous research and provides novel findings indicating that chronic smoking was associated with inferior performance on measures of general intelligence, visuospatial learning and memory and fine motor dexterity. Research that relates measures of neurobiological function/integrity to neurocognition is needed to better understand the mechanisms contributing to the poorer performance across multiple domains demonstrated by smokers.

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Conflict of Interest No conflict declared

Keywords

cigarette smoking; cognition; neurocognition; assessment; middle-age

1. Introduction

The majority of research on the neurocognitive consequences of chronic smoking has been conducted with adults greater than 60 years of age. Overall, the studies with those aged greater than 60 years indicate that chronic smoking is associated with deficiencies in auditory-verbal learning and memory, cognitive flexibility, executive functions, general intellectual abilities, processing speed, working memory and global cognitive function (Durazzo et al., 2010b). Compared to the amount of research conducted with elderly individuals, there are a limited number of studies on the neurocognitive effects of chronic smoking adults in the 30–60 year old age range (Durazzo et al., 2010b). This age range contains the greatest proportion of the population in the United States (U.S. Census Bureau, 2010), and, by extension, the greatest number of smokers (Dube et al., 2010). Specifically, the prevalence of smoking in the 30–60 age range is approximately 23% compared to 10% in those greater than 60 years of age (Dube et al., 2010). Previous cross-sectional studies with cohorts in 30–60 year age range indicated chronic smokers performed more poorly than non-smokers on measures of auditory-verbal learning and/or memory (Nooyens et al., 2008; Paul et al., 2006; Sabia et al., 2008), working memory (Ernst et al., 2001; George et al., 2002), executive functions (Ernst et al., 2001), processing speed (Richards et al., 2003), cognitive flexibility (Kalmijn et al., 2002; Nooyens et al., 2008) and postural stability (Iki et al., 1994). Higher pack years was related to lower global cognitive functioning (Schinka et al., 2002). The pattern of neurocognitive functioning demonstrated by smokers in the 30–60 age range parallels that observed in elderly cohorts. However, none of the foregoing studies with 30–60 year olds employed a battery that comprehensively and concurrently evaluated all the domains of functioning reported to be adversely affected by chronic cigarette smoking. Consequently, fine motor dexterity, static postural stability, general intellectual skills, visuospatial skills and visuospatial learning and memory were not consistently or robustly assessed in studies with adults in the 30–60 year age range. Additionally, few of these studies examined relationships between neurocognition and smoking severity (e.g., pack years, nicotine dependence). Therefore, the scope of neurocognitive dysfunction associated with chronic cigarette smoking in adults aged 30–60 years has yet to be fully delineated.

The primary goals of this prospective study were to: a) concurrently evaluate all neurocognitive domains of function that have been previously reported to be adversely affected by chronic smoking in healthy middle-aged adults (i.e., 30–60 years); and b) Investigate the relationships between neurocognition and measures of cigarette consumption/smoking chronicity. We predicted that: a) Smokers demonstrate inferior performance relative to non-smokers on measures of auditory-verbal and visuospatial learning and memory, executive skills, general intelligence, processing speed and working memory; and b) In smokers, longer duration of smoking over lifetime and higher pack years are related to poorer performance on these domains of function.

2. Methods

2.1. Participants

Twenty-seven non-smoking (four females) and 30 smoking (four females) community residing participants were recruited via posters, electronic billboards for a prospective study of the neurobiological and neurocognitive consequences of chronic cigarette smoking. All

participants were between the ages of 28 and 61 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.

Non-smoking participants were required to have smoked less than 20 cigarettes in their lifetime, no cigarette use in the 10 years prior to study and no history of use of other tobacco products. Smoking participants were required to be actively smoking at the time of assessment, smoke 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 enrollment. No smoking participant was engaged in any pharmacological/behavioral smoking nicotine cessation program or used other forms of tobacco at the time of study. The inclusion criteria for smokers were chosen because we were interested in studying the consequences of long-term chronic smoking on neurocognition (Durazzo et al., 2010b). Primary exclusion criteria are fully detailed in our previous work (Durazzo et al., 2007). In summary, participants were thoroughly screened (see section 2.2) 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) or psychiatric (i.e., mood, thought, anxiety, substance/alcohol use disorders) conditions known or suspected to influence neurocognition or brain neurobiology.

2.2. Medical, Psychiatric, Substance, Alcohol Consumption and Vocational Level 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 (Durazzo et al., 2004). Participants also 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 grams of pure ethanol) per month over 1 year prior to enrollment, average number of drinks per month over lifetime, and number of lifetime years of regular drinking (i.e., consuming at least one alcoholic drink per month). Participants complete 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), and nicotine dependence (Fagerstrom Tolerance Test for Nicotine Dependency (FTND); Fagerstrom et al., 1991). For smokers, the total number of cigarettes currently smoked per day, the number of years of smoking at the current level, total number of years smoking over lifetime were recorded and pack years (i.e., number of cigarettes per day/20 $\times$ total number of years of smoking) calculated. All participants were gainfully employed at the time of assessment and the highest attained vocational level/occupational was estimated with the 7-category Hollingshead scale of social position (Hollingshead 1975). Approximately 50% of participants of smokers and non-smokers 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 (i.e., THC, opiates, PCP, cocaine, and amphetamines) and they were evaluated for recent ethanol consumption via breathalyzer. No participant was positive for common illicit substances or ethanol consumption at the time of assessment.

2.3. Neurocognitive, Fine Motor and Postural Stability Assessment

Participants completed a comprehensive battery composed of well-normed measures that are commonly used in clinical and research settings in North America (see Strauss, Sherman and Spreen, 2006). Premorbid verbal intelligence was estimated with the American National Adult Reading Test (Grober and Sliwinski, 1991). The battery evaluated the domains of neurocognition and motor function reported to be adversely affected by chronic smoking as well as domains not rigorously assessed in previous research in the 30–60 age range (e.g., general intelligence, visuospatial learning and memory, fine motor dexterity) (Durazzo et al., 2010b; Swan and Lessov-Schlaggar, 2007). See Table 2 for the domains of functioning evaluated and the constituent measures. Smokers were allowed to smoke *ad libitum* prior to assessment and to take smoking breaks, if requested, to mitigate the potential for nicotine withdrawal effects on the abilities measured.

The cognitive efficiency domain consisted of all tests that were timed, or in which the time to complete the task influenced the score achieved, and was calculated by averaging the individual z-scores of those measures (see below). Timed tests included the Luria-Nebraska Item 99 ratio, Stroop word, color, and color-word tests, Trails A and B and WAIS-III Arithmetic, Block Design, Digit Symbol, Picture Completion, and Symbol Search. Higher scores on these measures reflect better speed and accuracy on principally non-verbal tasks. The cognitive efficiency domain is an approximation of the concept of cognitive efficiency described by Glen and Parsons (Glenn and Parsons, 1992) and Nixon and colleagues (Nixon et al., 1998; Nixon et al., 1995). For the Sharpened Romberg, a measure of static postural stability, participants were required to stand heel-to-toe, with arms crossed across the chest, for 60-seconds. Subjects first completed the task with eyes open and then with eyes closed. If a participant was unable to maintain the required position for at least 3 seconds on each of the four trials, the task was discontinued. If they successfully maintained this position for 60 seconds on any of the four trials they were given the maximum score of 60 for any remaining trials. For trials in which the 60-second criteria was not achieved, but the participant was able to maintain the required position for at least 3 seconds, the times were recorded and summed across trials to obtain the total score. Maximum possible score = 240 seconds. For the Luria-Nebraska Item 99, the number correct (maximum possible = 8) was divided by the time required to complete the task. This ratio was used due to the low ceiling for the number of correct responses (i.e., most participants achieved a score of 6 or better), which resulted in a highly skewed and non-Gaussian distribution. The distribution of the ratio of number correct to time to complete the Luria 99 did not deviate from normality.

Raw scores for all measures, except the Sharpened Romberg and Luria-Nebraska Item 99 ratio, were converted to *age-adjusted standardized scores* via the normative data accompanying the particular measure (i.e., BVMT-R, CVLT-II, Short Categories Test, Stroop Color-Word Test, WAIS-III subtests) or age and education (WCST-64 variables; Trails A and B, grooved pegboard via Heaton Compendium Norms; Heaton et al., 1991). Standardized scores were transformed to z-scores for all measures. For the Sharpened Romberg and Luria-Nebraska Item 99 ratio, raw scores were converted to z-scores based on the performance of non-smoking controls, as there are no published norms available for these measures. A global neurocognition score was formed by calculating the arithmetic average of z-scores for all of the individual neurocognitive domains.

2.4. Data Analyses

Multivariate analysis of covariance (MANCOVA) examined the effect of smoking status on the 11 neurocognitive domains. Primary models included education, AMNART, vocational level, lifetime average drinks per month as covariates as these factors are related to neurocognition (Durazzo and Meyerhoff, 2007; Heaton et al., 1991; Schretlen et al., 2005).

Although all neurocognitive scores forming the neurocognitive domains were based on age-adjusted standard scores, we also included age as a covariate with the above listed covariates in a second model to ensure age did not mediate any observed group differences. In exploratory analyses, a subgroup of non-smokers ($n = 17$) was matched to the smoker group on mean age, education, AMNART, lifetime average drinks per month, Hollingshead categories and sex (on all foregoing measures, smokers vs. non-smokers, $p > .38$). The objective was to compare (via MANOVA) the consistency of results obtained comparisons of smokers to non-smokers specifically equated on variables known to influence neurocognition and motor function to findings from the models based on MANCOVA that statistically controlled for the effects of such factors. Significant MANCOVA/MANOVA omnibus effects of smoking status ($p < .05$) were followed up with pairwise t-tests. Although we predicted smokers would show an inferior performance to non-smokers on the domains of auditory-verbal and visuospatial learning and memory, executive skills, general intelligence, processing speed and working memory, we chose the conservative approach of adjusting alpha levels ($p = .05$, two-tailed) for all pairwise group comparisons across domains for multiplicity of tests. Specifically, pairwise t-tests were adjusted for the number of neurocognitive domains evaluated (i.e., 11) and the average intercorrelation among all the domains (i.e., $r = 0.51$), resulting in a corrected p-level $\leq .015$ (Sankoh et al., 1997). A separate analysis of covariance (ANCOVA) was conducted for fine motor dexterity, controlling for, AMNART, vocational level, and lifetime average drinks per month. Age and education were not used as a covariate because measures contributing to this domain were corrected for age and education via normative data. The Mann-Whitney U test was used to compare groups on the Sharpened Romberg test because the eyes open and eyes closed trials showed highly skewed, non-normal distributions; log transformation did not produce a Gaussian distribution for either trial. P-values of $\leq .015$ (two-tailed) were considered statistically significant for the pairwise t-test for the Sharpened Romberg test trails and fine motor dexterity. Effect sizes (ES) for pairwise comparisons were calculated via Cohen's d (Cohen, 1988). Domains that showed significant differences between smokers and non-smokers in pairwise comparisons were used as factors in a binary logistic regression to predict smoking status (i.e., smoker or non-smoker) and determine the sensitivity and specificity of these domains in classifying smokers and non-smokers into their respective groups. Relationships between alcohol consumption (over 1 year and lifetime), body mass index (BMI), BDI, STAI scores and domains were examined with Spearman's rho independently for smokers and non-smokers and for the combined sample. In smokers, relationships between smoking consumption measures (i.e., lifetime years of smoking, FTND score, pack years, cigarettes smoked/day) and domains were examined with multiple linear regression (semi-partial coefficients reported) controlling for lifetime average drinks per month. False discovery rate (FDR) was used to adjust p-values for the foregoing correlational analyses for multiplicity of tests (Benjamini and Hochberg, 1995) and a FDR corrected p-value $\leq .05$ was considered statistically significant. All analyses were completed with SPSS v18.0.

3. Results

3.1. Demographics, Alcohol and Cigarette Use and Clinical Measures

Seventy-one percent of participants were Caucasian, 13% African American, 11% Asian and 5% Latino. Groups were not different on ethnicity frequency, Hollingshead vocational level, average number of drinks per month 1-year prior to enrollment, gender or AMNART, BDI, BMI and STAI scores. Smokers were significantly younger ($p = .049$), had significantly lower level of formal education ($p = .004$) and higher lifetime average number of drinks per ($p = .008$) than non-smokers (See Table 1).

3.2. Group Comparisons on Domains

The omnibus MANCOVA indicated smoking status (i.e., smoker vs. non-smoker; $F(11, 41) = 4.89, p < .001$) and Hollingshead vocational level ($F(11, 41) = 3.43, p = .002$) were significant predictors across domains of neurocognition. Age ($p = .13$), AMNART ($p = .17$), education ($p = .51$), lifetime average drinks per month ($p = .25$) were not significant predictors. No multicollinearity was apparent among the above predictors for any domain. Smokers were inferior to non-smokers on the following domains (all $p < .015$): auditory-verbal learning, cognitive efficiency, executive skills, fine motor dexterity, general intelligence, postural stability, processing speed, visuospatial learning and memory and global neurocognition (see Table 3). Trends for poorer performance for smokers were observed for auditory-verbal memory ($p = .017$) and visuospatial skills ($p = .022$). Hollingshead vocational level was a significant predictor of the following domains (all $p < .015$): auditory-verbal learning and memory, cognitive efficiency, executive skills, visuospatial skills and global neurocognition; higher vocational level was associated with better scores on these domains. On measures of postural stability, no group differences were observed on the eyes open trial of the Sharpened Romberg ($p = .99$) as all participants in each group achieved the maximum score, but smokers were inferior on the eyes closed trial ($p < .001$). The performance of the females on across domains was within ± 0.5 standard deviations of male participants. Findings for analyses comparing all smokers ($n = 30$) to non-smokers ($n = 17$) matched on age, education, AMNART, vocational level, alcohol consumption and sex yielded a virtually identical pattern of group differences across domains (all $p < .015$) and corresponding effect sizes as those reported above (data not shown).

We intended to enter all domains that were significantly different between groups into a binary logistic regression in order to determine the sensitivity and specificity of these variables in the prediction of smoking status. However, global neurocognition domain demonstrated a high level of multicollinearity, so it was excluded as a predictor. In logistic regression models, it is recommended that the ratio of participants to predictors to exceed 10:1 to decrease the risk of both overfitting (Babyak, 2004). To follow this guideline and mitigate multicollinearity among individual predictors, we reduced the number of domains through forming three new predictors by taking the average for: 1) auditory-verbal learning, visuospatial learning and visuospatial memory; 2) cognitive efficiency and processing speed; 3) fine motor dexterity and postural stability. These three factors plus executive skills and general intelligence were used as predictors of smoking status (i.e., smoker, non-smoker). The combination of these factors significantly predicted smoking status ($\chi^2(5) = 36.3, p < 0.001$). These five predictors accurately classified 90% (27 of 30) smokers (i.e., sensitivity) and 89% (24 of 27) non-smokers (i.e., specificity) and accounted for 67% of the variance in smoking status. No multicollinearity was apparent among predictors. Given that Hollingshead vocational level was a robust predictor of multiple domains of neurocognition, it was added as a predictor to the five predictors above to determine if it increased model explanatory power and accuracy of fit. The addition of Hollingshead vocational level did not significantly improve explanatory power and accuracy of fit of the model or group classification accuracy (data not shown).

3.3. Associations of Domains with Clinical, Alcohol and Cigarette Use Measures

In the combined group (smokers + non-smokers) and for each group individually, there were no significant relationships between BMI, BDI, STAI, average drinks per month over 1-year prior to enrollment or lifetime and any domain. In smokers, after controlling for lifetime average drinks per month, greater number of lifetime years of smoking was related to poorer cognitive efficiency ($r = -0.41; p = .044$), processing speed ($r = -0.44; p = .041$), and visuospatial skills ($r = -0.40; p = .049$) (see Figures 1 and 2). There was a trend for an

association between lifetime years of smoking and poorer postural stability on the eyes closed trail ($\rho = -.40$; $p = .055$). There were no significant relationships between pack years, cigarettes smoked per day or FTND score and any domain in smokers.

4. Discussion

Results from this prospective study with healthy, primarily Caucasian, middle-aged individuals indicated that chronic smoking was associated with significantly poorer performance on measures of executive skills, fine motor dexterity, general intelligence, processing speed, static postural stability, auditory-verbal and visuospatial learning and visuospatial memory. The inferior performance of smokers on measures of fine motor dexterity, general intelligence and visuospatial learning and memory are novel as these domains were not specifically evaluated in earlier studies with middle-aged samples. Importantly, the group differences showed moderate to strong effect sizes after statistically controlling for, or equating non-smokers to smokers, on age, education, predicted premorbid verbal IQ (i.e., AMNART), vocational level and alcohol consumption. The domains that were significantly different between groups also demonstrated a high level of sensitivity and specificity in the prediction of smoking status (i.e., smoker, non-smoker). In smokers, greater lifetime years of smoking was related to poorer processing speed, cognitive efficiency and visuospatial skills. The alcohol consumption of both groups did not approach a “hazardous” level of use (McKee et al., 2007; Mertens et al., 2005) and groups were free of medical, psychiatric and substance/alcohol conditions (according to self-report) that are known to influence neurocognition and motor function.

With respect to level of functioning, the mean performance of smokers was in the average range of functioning (25th to 66th percentile) on auditory-verbal learning and memory, cognitive efficiency, executive skills, fine motor dexterity, processing speed, visuospatial skills and working memory, and in the low average range for postural stability (20th percentile), visuospatial learning (11th percentile) and visuospatial memory (16th percentile). The mean performance of non-smokers was in the average range across domains (50th to 69th percentile) except for auditory-verbal learning (82nd percentile) and general intelligence (79th percentile), which were both in the high average range.

There were moderate to large magnitude differences between smokers and non-smokers in this study on functions that were not expressly assessed in previous research with individuals in the 30–60 age range, specifically on fine motor dexterity, full scale general intelligence and visuospatial learning and memory (see Table 3). For fine motor dexterity, the greatest difference between smokers and non-smokers was apparent for the non-dominant hand. The inferior performance of smokers on the general intelligence domain was primarily driven by poorer performance on non-verbal measures contributing to the WAIS-III Performance IQ scale. There was also a substantial disparity in ability for smokers compared to non-smokers on visuospatial learning and memory. The smokers' visuospatial learning and memory was well below their performance on other neurocognitive domains and unexpected given their level of education and estimated premorbid verbal IQ (i.e., AMNART score). The inferior performance of smokers relative to non-smokers on measures of auditory-verbal learning and memory, executive skills, processing speed and static postural stability are consistent with previous studies with middle-aged cohorts (Ernst et al., 2001; Iki et al., 1994; Kalmijn et al., 2002; Nooyens et al., 2008; Paul et al., 2006; Richards et al., 2003; Sabia et al., 2008). Yet, the magnitude of differences between smokers and non-smokers in this study appears to be greater than previous reports (e.g., Kalmijn et al., 2002; Nooyens et al., 2008; Paul et al., 2006; Schinka et al., 2002), despite generally similar levels of smoking severity (e.g., pack years, cigarettes smoked/day). This may be related to the greater number and breadth of measures that contributed to the domains

assessed in the current study, which permitted a more comprehensive evaluation of functions potentially affected by chronic smoking. Additionally, the domain scores that are composed of multiple measures are the arithmetic average of the constituent measures. Therefore, it is highly unlikely that a single measure could account for the domain effect sizes observed in this study.

The findings for smokers and non-smokers in this study also showed remarkable consistency with our research on the effects of chronic smoking in middle-aged adults with alcohol use disorders. Using an identical assessment battery to that employed in this study, we observed in those with alcohol use disorders that chronic smokers performed significantly worse than non-smokers on measures of cognitive efficiency, executive skills, processing speed, static postural stability and auditory-verbal and visuospatial learning and memory after controlling for alcohol consumption and other potentially confounding comorbid conditions. Additionally, greater lifetime years of smoking was related poor performance on measures of cognitive efficiency, processing speed and postural stability in our middle-aged alcohol dependent participants after controlling for alcohol consumption (Durazzo et al., 2010a; Durazzo et al., 2006; Durazzo et al., 2008), which is consistent with results from the current study. The results of this study are also congruent with the findings other studies that reported chronic smoking in adults with alcohol use disorders is independently associated with diminished neurocognitive function (Friend et al., 2005; Glass et al., 2005; Glass et al., 2009).

There are several potential chronic smoking-related biological mechanisms that may work independently, or in concert, to promote the neurocognitive and neurobiological abnormalities demonstrated by smokers (Durazzo et al., 2010b; Swan and Lessov-Schlaggar, 2007). However, it is important to note that although the differences observed *between* smokers and non-smokers were not mediated by age, education, AMNART, vocational level or alcohol consumption, *within* the smoker group only greater lifetime years of smoking was significantly related to poorer performance on cognitive efficiency, processing speed and visuospatial skills. Additionally, no significant associations were observed between other smoking measures (e.g., pack years, level of nicotine dependence) and domain performance in smokers after correction for multiple tests. Therefore, it is possible that the inferior performance demonstrated by smokers on several domains may be, at least partially, influenced by premorbid factors and/or related to comorbid factors not assessed in this study. If certain domains show no dose/duration-response with smoking, they may potentially serve as markers for increased risk of development of nicotine dependence (Tessner and Hill, 2010).

This report has limitations that may influence the generalizability of the findings. Medical, psychiatric and alcohol/substance histories were based on self-report and we did not assess for personality disorders, which may mediate aspects neurocognition (Costa et al., 2000; Eckardt et al., 1995; Giancola and Moss, 1998; Kuruoglu et al., 1996). Although we controlled for estimated premorbid verbal IQ, education and vocational level in group comparisons, the measured general intellectual differences between smokers and non-smokers could reflect different premorbid ability, which may have influenced the pattern of findings. Additionally, group performances were potentially influenced by factors not directly assessed in this study such as nutrition, exercise, and previous exposure to environmental cigarette smoke or premorbid/genetic predispositions. The majority of participants were males, which did not allow for the examination for sex effects. Additionally, it is not possible to use covariates with non-parametric tests such as the Mann-Whitney U; consequently, we were unable to control group comparisons on measures of postural stability for lifetime average drinks per month, age and education. Although these factors were not significantly correlated with postural stability in the sample, we cannot

unequivocally conclude that the poorer postural stability demonstrated by smokers was independent of the effects of alcohol consumption, age or education. Despite our conservative statistical approach, the modest sample size of this study requires that the reported findings be considered preliminary in nature.

In conclusion, results from this primarily Caucasian male, middle-aged cohort replicated previous research and presents novel findings indicating that chronic smoking is associated with inferior performance on measures of fine motor dexterity, general intelligence and visuospatial learning and memory. The inferior performance demonstrated by smokers was not a function of age, education, estimated premorbid verbal IQ, vocational level and alcohol consumption. Longitudinal research with larger samples is necessary to examine for other potential premorbid/comorbid factors associated with neurocognitive performance in smokers and to determine if continued smoking is related to with further deterioration in these abilities over time. Additional research that relates measures of brain neurobiological function/integrity to neurocognition is needed to better understand the mechanisms contributing to the poorer performance across multiple domains demonstrated by smokers. Irrespective of the potential mechanism(s) leading to the observed group differences, a history of chronic smoking during midlife is associated with greater cognitive decline in those ≥ 64 years of age (Deary et al., 2003; Starr et al., 2006; Whalley et al., 2005) as well as strongly linked to increased risk for Alzheimer Disease (Anstey et al., 2007; Cataldo and Glantz, 2010; Rusanen et al., 2010). This information combined with the substantial mortality and morbidity associated with chronic smoking stresses the need for development of more efficacious behavioral and pharmacological treatments to facilitate sustained smoking cessation as well as greater emphasis on smoking prevention programs for adolescents and young adults.

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References

- 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. *Am. J. Epidemiol.* 2007; 166:367–378. [PubMed: 17573335]
- Axelrod BN, Ryan JJ, Ward LC. Evaluation of seven-subtest short forms of the Wechsler Adult Intelligence Scale-III in a referred sample. *Arch. Clin. Neuropsychol.* 2001; 16:1–8. [PubMed: 14590188]
- Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom. Med.* 2004; 66:411–421. [PubMed: 15184705]
- Beck, AT. *Depression Inventory*. Center for Cognitive Therapy; Philadelphia: 1978.
- Benedict, R. *Brief Visuospatial Memory Test - Revised: Professional Manual*. Psychological Assessment Resources, Inc.; Odessa, FL: 1997.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. Royal Stat. Soc.* 1995; 57:289–300.
- Cataldo JK, Glantz SA. Smoking cessation and Alzheimer's disease: facts, fallacies and promise. *Expert. Rev. Neurother.* 2010; 10:629–631. [PubMed: 20420482]
- Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum Associates; Hillsdale, NJ: 1988.

- Costa L, Bauer L, Kuperman S, Porjesz B, O'Connor S, Hesselbrock V, Rohrbaugh J, Begleiter H. Frontal P300 decrements, alcohol dependence, and antisocial personality disorder. *Biol. Psychiatry*. 2000; 47:1064–1071. [PubMed: 10862806]
- Deary IJ, Pattie A, Taylor MD, Whiteman MC, Starr JM, Whalley LJ. Smoking and cognitive change from age 11 to age 80. *J. Neurol. Neurosurg. Psychiatry*. 2003; 74:1003–1007. [PubMed: 12810808]
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test. 2nd Edition. The Psychological Corporation; San Antonio, TX: 2000.
- Dube SR, McClave A, James C, Caraballo R, Kaufmann R, Pechacek T. Vital signs: current cigarette smoking among adults aged ≥ 18 years --- United States, 2009. *MMWR*. 2010; 59:1135–40. [PubMed: 20829747]
- Durazzo TC, Fryer SL, Rothlind JC, Vertinski M, Gazdzinski S, Mon A, Meyerhoff DJ. Measures of learning, memory and processing speed accurately predict smoking status in short-term abstinent treatment-seeking alcohol-dependent Individuals. *Alcohol Alcohol*. 2010a; 45:507–513. [PubMed: 20923865]
- Durazzo TC, Gazdzinski S, Banys P, Meyerhoff DJ. Cigarette smoking exacerbates chronic alcohol-induced brain damage: a preliminary metabolite imaging study. *Alcohol. Clin. Exp. Res*. 2004; 28:1849–1860. [PubMed: 15608601]
- Durazzo TC, Meyerhoff DJ. Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. *Front. Biosci*. 2007; 12:4079–4100. [PubMed: 17485360]
- Durazzo TC, Meyerhoff DJ, Nixon SJ. Chronic cigarette smoking: implications for neurocognition and brain neurobiology. *Int. J. Environ. Res. Public. Health*. 2010b; 7:3760–3791. [PubMed: 21139859]
- Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. A comparison of neurocognitive function in nonsmoking and chronically smoking short-term abstinent alcoholics. *Alcohol*. 2006; 39:1–11. [PubMed: 16938624]
- Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. Chronic smoking is associated with differential neurocognitive recovery in abstinent alcoholic patients: a preliminary investigation. *Alcohol. Clin. Exp. Res*. 2007; 31:1114–1127. [PubMed: 17451399]
- Durazzo TC, Rothlind JC, Gazdzinski S, Meyerhoff DJ. The relationships of sociodemographic factors, medical, psychiatric, and substance-misuse co-morbidities to neurocognition in short-term abstinent alcohol-dependent individuals. *Alcohol*. 2008; 42:439–449. [PubMed: 18760713]
- Eckardt MJ, Stapleton JM, Rawlings RR, Davis EZ, Grodin DM. Neuropsychological functioning in detoxified alcoholics between 18 and 35 years of age. *Am. J. Psychiatry*. 1995; 152:53–59. [PubMed: 7802120]
- Ernst M, Heishman SJ, Spurgeon L, London ED. Smoking history and nicotine effects on cognitive performance. *Neuropsychopharmacology*. 2001; 25:313–319. [PubMed: 11522460]
- Fagerstrom KO, Heatherton TF, Kozlowski LT. Nicotine addiction and its assessment. *Ear Nose Throat J*. 1991; 69:763–765. [PubMed: 2276350]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. 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: 1998.
- Fregly AR, Graybiel A. An ataxia test battery not requiring rails. *Aerospace Med*. 1968; 39:277–282. [PubMed: 5636011]
- Friend KB, Malloy PF, Sindelar HA. The effects of chronic nicotine and alcohol use on neurocognitive function. *Addict. Behav*. 2005; 30:193–202. [PubMed: 15561461]
- George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, Kosten TR, Wexler BE. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology*. 2002; 26:75–85. [PubMed: 11751034]
- Giancola PR, Moss HB. Executive cognitive functioning in alcohol use disorders. *Recent Dev. Alcohol*. 1998; 14:227–251. [PubMed: 9751948]
- Glass JM, Adams KM, Nigg JT, Wong MM, Puttler LI, Buu A, Jester JM, Fitzgerald HE, Zucker RA. Smoking is associated with neurocognitive deficits in alcoholism. *Drug Alcohol Depend*. 2005; 82:119–126. [PubMed: 16169161]

- Glass JM, Buu A, Adams KM, Nigg JT, Puttler LI, Jester JM, Zucker RA. Effects of alcoholism severity and smoking on executive neurocognitive function. *Addiction*. 2009; 104:38–48. [PubMed: 19133887]
- Glenn SW, Parsons OA. Neuropsychological efficiency measures in male and female alcoholics. *J. Stud. Alcohol*. 1992; 53:546–552. [PubMed: 1434630]
- Golden, CJ. Stroop Color and Word Test. Stoelting Company; Chicago, IL: 1978.
- Golden CJ, Hammeke TA, Purisch AD. Diagnostic validity of a standardized neuropsychological battery derived from Luria's neuropsychological tests. *J. Consult. Clin. Psychol*. 1978; 46:1258–1265. [PubMed: 730876]
- Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *J. Clin. Exp. Neuropsychol*. 1991; 13:933–949. [PubMed: 1779032]
- Heaton, RK.; Grant, I.; Matthews, CG. Comprehensive Norms for an Expanded Halstead-Reitan Battery Demographic Corrections, Research Findings, and Clinical Applications. Psychological Assessment Resources, Inc.; Odessa, FL: 1991.
- Iki M, Ishizaki H, Aalto H, Starck J, Pykko I. Smoking habits and postural stability. *Am. J. Otolaryngol*. 1994; 15:124–128. [PubMed: 8179103]
- Kalmijn S, van Boxtel MP, Verschuren MW, Jolles J, Launer LJ. Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. *Am. J. Epidemiol*. 2002; 156:936–944. [PubMed: 12419766]
- Kongs, S.; Thompson, L.; Iverson, G.; Heaton, RK. WCST-64: Wisconsin Card Sorting Test-64 Card Version, Professional Manual. Psychological Assessment Resources, Inc.; Lutz, FL: 2000.
- Kuruoglu AC, Arian Z, Vural G, Karatas M, Arac M, Isik E. Single photon emission computerised tomography in chronic alcoholism. Antisocial personality disorder may be associated with decreased frontal perfusion. *Br. J. Psychiatry*. 1996; 169:348–354. [PubMed: 8879722]
- McKee SA, Falba T, O'Malley SS, Sindelar J, O'Connor PG. Smoking status as a clinical indicator for alcohol misuse in US adults. *Arch. Intern. Med*. 2007; 167:716–721. [PubMed: 17420431]
- Mertens JR, Weisner C, Ray GT, Fireman B, Walsh K. Hazardous drinkers and drug users in HMO primary care: prevalence, medical conditions, and costs. *Alcohol. Clin. Exp. Res*. 2005; 29:989–998. [PubMed: 15976525]
- Nixon SJ, Paul R, Phillips M. Cognitive efficiency in alcoholics and polysubstance abusers. *Alcohol. Clin. Exp. Res*. 1998; 22:1414–1420. [PubMed: 9802522]
- Nixon SJ, Tivis R, Parsons OA. Behavioral dysfunction and cognitive efficiency in male and female alcoholics. *Alcohol. Clin. Exp. Res*. 1995; 19:577–581. [PubMed: 7573777]
- Nooyens AC, van Gelder BM, Verschuren WM. Smoking and cognitive decline among middle-aged men and women: the Doetinchem Cohort Study. *Am. J. Public Health*. 2008; 98:2244–2250. [PubMed: 18923116]
- Paul RH, Brickman AM, Cohen RA, Williams LM, Niaura R, Pogun S, Clark CR, Gunstad J, Gordon E. Cognitive status of young and older cigarette smokers: data from the International Brain Database. *J. Clin. Neurosci*. 2006; 13:457–465. [PubMed: 16678725]
- Reitan, RM.; Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Interpretation. Neuropsychological Press; Tucson, AZ: 1985.
- Richards M, Jarvis MJ, Thompson N, Wadsworth ME. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. *Am. J. Public Health*. 2003; 93:994–998. [PubMed: 12773367]
- 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*. 2011; 171:333–339. [PubMed: 20975015]
- Sabia S, Marmot M, Dufouil C, Singh-Manoux A. Smoking history and cognitive function in middle age from the Whitehall II study. *Arch. Intern. Med*. 2008; 168:1165–1173. [PubMed: 18541824]
- Sankoh AJ, Huque MF, Dubey SD. Some comments on frequently used multiple endpoint adjustment methods in clinical trials. *Stat. Med*. 1997; 16:2529–2542. [PubMed: 9403954]
- Schinka JA, Vanderploeg RD, Rogish M, Ordorica PI. Effects of alcohol and cigarette use on cognition in middle-aged adults. *J. Int. Neuropsychol. Soc*. 2002; 8:683–690. [PubMed: 12164677]

- Schretlen DJ, Buffington AL, Meyer SM, Pearlson GD. The use of word-reading to estimate premorbid ability in cognitive domains other than intelligence. *J. Int. Neuropsychol. Soc.* 2005; 11:784–787. [PubMed: 16248914]
- Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. *J. Stud. Alcohol.* 1982; 43:1157–1170. [PubMed: 7182675]
- Sobell LC, Sobell MB, Riley DM, Schuller R, Pavan DS, Cancilla A, Klajner F, Leo GI. The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past. *J. Stud. Alcohol.* 1988; 49:225–232. [PubMed: 3374136]
- Spielberger, CD.; Gorsuch, RL.; Lushene, R.; Vagg, PR.; Jacobs, GA. Self-Evaluation Questionnaire. Consulting Psychologist Press; Palo Alto, CA: 1977.
- Strauss, E.; Sherman, EMS.; Spreen, O. A compendium of neuropsychological tests. Oxford, New York; New York: 2006.
- Starr JM, Deary IJ, Fox HC, Whalley LJ. Smoking and cognitive change from age 11 to 66 years: a confirmatory investigation. *Addict. Behav.* 2006; 32:63–68. [PubMed: 16650620]
- Swan GE, Lessov-Schlaggar CN. The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychol. Rev.* 2007; 17:259–273. [PubMed: 17690985]
- Tessner KD, Hill SY. Neural circuitry associated with risk for alcohol use disorders. *Neuropsychol. Rev.* 2010; 20:1–20. [PubMed: 19685291]
- Wechsler, D. The Wechsler Adult Intelligence Scale. Third Edition. The Psychological Corporation; San Antonio, TX: 1997.
- Wetzel, L.; Boll, TJ. Short Category Test, Booklet Format. Western Psychological Services; Los Angeles: 1987.
- Whalley LJ, Fox HC, Deary IJ, Starr JM. Childhood IQ, smoking, and cognitive change from age 11 to 64 years. *Addict. Behav.* 2005; 30:77–88. [PubMed: 15561450]

Figure 1.
Relationship between lifetime years of smoking and cognitive efficiency

Figure 2.
Relationship between lifetime years of smoking and processing speed

Figure 3.
Relationship between lifetime years of smoking and visuospatial skills

Table 1

Demographic and Clinical Measures

Variable	Non-smokers (n = 27)	Smokers (n = 30)
Age	44.4 (8.7)	48.9 (8.4) *
Education	15.8 (2.0)	14.4 (1.6) *
%Caucasian	70	72
Hollingshead SES [mean (SD)/mode]	2.81 (1.1)/3	3.13 (1.0)/3
AMNART	119 (6.3)	116 (6.0)
BDI	3.7 (3.4)	4.1 (3.1)
STAI-trait	32.2 (7.8)	33.0 (6.8)
1-yr avg drinks/month	13.9 (16.1)	19.7 (21.0)
Lifetime avg drinks/month	15.1 (13.3)	25.4 (13.1) *
FTND	NA	5.0 (1.4)
Cigarettes/day	NA	20.4 (5.5)
Age onset of regular smoking	NA	19.5 (7.1)
Total lifetime years of smoking	NA	29.1 (10.0)
Pack years	NA	29.8 (14.0)
Body mass index	26.2 (4.8)	27.9 (8.1)

Note.

AMNART: American National Adult Reading Test; BDI: Beck Depression Inventory; FTND: Fagerstrom Test for Nicotine Dependence; SES: Socioeconomic status STAI State-Trait Anxiety Inventory. Mean (SD).

*
p < .05;

Table 2

Domains and Constituent Measures

Domain	Constituent Measures
Auditory-verbal learning	California Verbal Learning Test-II (Delis et al., 2000), Immediate Recall trials 1–5
Auditory-verbal memory	CVLT-II Short and Long Delay Free Recall
Cognitive efficiency	This domain consisted of all tests that were timed, or the time to complete the task influenced the score obtained (see Methods for details)
Executive skills	<ul style="list-style-type: none"> • Short Categories Test (Wetzel and Boll, 1987) • Stroop Test, color-word subtest (Golden, 1978) • Trail Making Test part B (Reitan and Wolfson, 1985) • Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) Similarities (Wechsler, 1997) • Wisconsin Card Sorting Test-64: Computer Version 2-Research Edition (Kongs et al., 2000), non-perseverative errors, perseverative errors, perseverative responses
Fine motor dexterity	Grooved Pegboard Test (Lafayette Instrument, Lafayette IN)
Postural stability	Sharpened Romberg test from the Modified Fregly Ataxia Battery, (Fregly and Graybiel, 1968). See Methods for details.
General intelligence	<p>Ward-7 Full Scale IQ [(Axelrod et al., 2001), based on the following WAIS-III subtests:</p> <ul style="list-style-type: none"> • Arithmetic • Block Design, • Digit Span, • Digit Symbol, • Information • Picture Completion • Similarities
Processing speed	<ul style="list-style-type: none"> • Stroop Test, color & word subtests (Golden, 1978) • Trail Making Test part A (Reitan and Wolfson, 1985) • WAIS-III Digit Symbol • WAIS-III Symbol Search
Visuospatial learning	Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997), Total Recall (learning trials 1–3)
Visuospatial memory	BVMT-R Delayed Recall
Visuospatial skills	<ul style="list-style-type: none"> • Luria-Nebraska Item 99 (Golden et al., 1978) • WAIS-III Block Design
Working memory	<ul style="list-style-type: none"> • WAIS-III Arithmetic • WAIS-III Digit Span

Table 3

Domain z-scores

Neurocognitive	Non-smokers (n = 27)	Smokers (n = 30)	Effect Size (Cohen's <i>d</i>)
Auditory-verbal learning	0.99 (0.70)	0.29 (0.69)*	1.11
Auditory-verbal memory	0.52 (0.75)	0.01 (0.74)	0.68
Cognitive efficiency	0.20 (0.50)	−0.29 (0.49)*	0.99
Executive skills	0.19 (0.61)	−0.51 (0.61)*	1.15
General intelligence	0.81 (0.75)	0.24 (0.76)*	0.76
Processing speed	0.25 (0.46)	−0.15 (0.46)*	0.85
Visuospatial learning	0.01 (0.98)	−1.26 (0.99)*	1.29
Visuospatial memory	0.20 (1.01)	−0.97 (1.02)*	1.14
Visuospatial skills	0.31 (0.90)	−0.25 (0.89)	0.61
Working memory	0.45 (0.71)	0.33 (0.72)	0.16
Global neurocognition	0.38 (0.48)	−0.26 (0.48)*	1.32
Fine motor and Postural Stability			
Fine motor dexterity	0.01 (0.98)	−0.66 (0.87)*	0.72
Postural stability	0.00 (1.00)	−0.86 (1.36)*	0.73

Note.

* Smokers < non-smokers, $p \leq .015$. Mean (SD).