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Chronic Cigarette Smoking in Healthy Middle-Aged Individuals Is Associated With Decreased Regional Brain *N*-acetylaspartate and Glutamate Levels

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ABSTRACT

BACKGROUND: Cigarette smoking is associated with metabolite abnormalities in anterior brain regions, but it is unclear if these abnormalities are apparent in other regions. Additionally, relationships between regional brain metabolite levels and measures of decision making, risk taking, and impulsivity in smokers and nonsmokers have not been investigated.

METHODS: In young to middle-aged (predominately male) nonsmokers (n = 30) and smokers (n = 35), *N*-acetylaspartate (NAA), choline-containing compounds, creatine-containing compounds (Cr), *myo*-inositol (mI), and glutamate (Glu) levels in the anterior cingulate cortex and right dorsolateral prefrontal cortex (DLPFC) were compared via 4-tesla proton single volume magnetic resonance spectroscopy. Groups also were compared on NAA, choline-containing compounds, Cr, and mI concentrations in the gray matter and white matter of the four cerebral lobes and subcortical nuclei/regions with 1.5-tesla proton magnetic resonance spectroscopy. Associations of regional metabolite levels with neurocognitive, decision-making, risk-taking, and self-reported impulsivity measures were examined.

RESULTS: Smokers showed lower DLPFC NAA, Cr, mI and Glu concentrations and lower lenticular nuclei NAA level; smokers also demonstrated greater age-related decreases of DLPFC NAA and anterior cingulate cortex and DLPFC Glu levels. Smokers exhibited poorer decision making and greater impulsivity. Across the sample, higher NAA and Glu in the DLPFC and NAA concentrations in multiple lobar gray matter and white matter regions and subcortical nuclei were associated with better neurocognition and lower impulsivity.

CONCLUSIONS: This study provides additional novel evidence that chronic smoking in young and middle-aged individuals is associated with significant age-related neurobiological abnormalities in anterior frontal regions implicated in the development and maintenance of addictive disorders.

Keywords: Brain metabolites, Cigarette smoking, Decision making and impulsivity, Magnetic resonance, Neurocognition, Spectroscopy

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Chronic cigarette smoking in adults is associated with multiple neurobiological and neurocognitive abnormalities (1–3). The majority of earlier [see (1)] and recent (4–10) studies on smoking-related neurobiological abnormalities employed magnetic resonance imaging (MRI)–based morphologic measures (i.e., volume and cortical thickness). Overall, the findings indicated that smokers demonstrate widespread structural abnormalities that are particularly prominent in anterior frontal lobe subregions (11).

Although MRI morphometry provides fundamental information on the macroscopic viability of regional brain tissue, magnetic resonance spectroscopy enables a more direct interrogation of the functional integrity of brain tissue. Single volume proton magnetic resonance spectroscopy (SVS) and spectroscopic imaging (SI) methods allow the noninvasive and concurrent quantitation of several brain metabolites that collectively provide information regarding the neurophysiologic viability of tissue (12,13). Abnormalities in certain metabolite concentrations (e.g., *N*-acetyl aspartate [NAA], choline-containing compounds [Cho]) may precede macroscopic morphologic or neurocognitive changes associated with some diseases or conditions (13). The brain metabolites most commonly quantitated via SVS and SI methods include biomarkers of neuronal integrity (i.e., NAA), cell membrane turnover and synthesis (i.e., Cho), cellular bioenergetics (i.e., creatine-containing compounds [Cr]), astrogliosis and inflammation (i.e., *myo*-inositol [mI]), and excitatory neurotransmitter and neuromodulator pools (i.e., glutamate [Glu]) (13,14). Higher regional NAA and Glu levels are associated with better function in multiple neurocognitive domains (15,16), and both of these metabolites show age-dependent decreases in concentration across adulthood (13). The few proton magnetic resonance spectroscopy studies of "healthy" chronic smokers

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primarily employed SVS at 3 tesla (T) and focused on anterior frontal regions (e.g., anterior cingulate cortex [ACC], dorsolateral prefrontal cortex [DLPFC]) and the hippocampus in young or middle-aged adults; anterior frontal subregions and the hippocampus were emphasized because neurobiological abnormalities in these regions are implicated in the development and persistence of addictive disorders (17,18).

Gallinat *et al.* (19) reported that smokers showed lower NAA levels than nonsmokers in the left hippocampus, and higher pack-years were related to higher Cho levels in the anterior cingulate gyrus; however, in a subsequent study, the same investigators found no differences between active smokers, former smokers, and nonsmokers on Glu levels in the ACC and left hippocampus (20). O'Neill *et al.* (21) found no differences between smokers and nonsmokers in thalamic Glu concentration, but among smokers, more cigarettes smoked per day and pack-years of smoking were strongly related to lower thalamic Glu level. Mennecke *et al.* (22) reported higher left anterior cingulate Glu/glutamine and Cho concentrations in smokers than nonsmokers; after 3 days of smoking cessation, anterior cingulate glutamine decreased to nonsmoker levels, but no changes were observed for Cho. In the sole SI study, Durazzo *et al.* (23) observed that a small group of smokers had lower Cho concentrations in the cerebellar vermis than nonsmokers. Taken together, these studies provide evidence that chronic smoking is associated with regional derangements of cortical NAA, Cho, and glutamine levels. However, a limitation of the SVS method is that it does not simultaneously measure metabolites across a large number of brain regions; the regional specificity of the metabolic findings in chronic smokers (e.g., anterior vs. parietal, temporal, or subcortical) and their tissue specificity (i.e., gray matter [GM] vs. white matter [WM]) is unclear. Additionally, previous studies did not assess associations between the regional brain metabolite levels and measures of neurocognition, decision making, risk taking, or impulsivity; consequently, the functional relevance of the metabolite abnormalities observed in smokers is uncertain.

This study compared regional brain metabolite levels in healthy middle-aged smokers and nonsmokers. Imaging with SVS at 4T measured NAA, Cho, Cr, mI, and Glu levels in the right DLPFC and the bilateral ACC; studies at 4T facilitate more accurate quantitation of the Glu signal than lower field strengths because of greater spectral dispersion and increased signal-to-noise ratio (13). Additionally, SI at 1.5T simultaneously measured NAA, Cho, Cr, and mI (but not Glu) concentrations in the GM and WM of the bilateral frontal, parietal, and temporal lobes; occipital WM; and lenticular nucleus, thalamus, and cerebellar vermis. Associations of SVS and SI metabolite levels with performance on a comprehensive neurocognitive battery and on measures of impulsivity, decision making, and risk taking were examined.

Chronic smoking, independent of common smoking-related diseases (e.g., cerebrovascular disease, chronic obstructive pulmonary disorders), appears to affect adversely the integrity of brain neurobiology (1). Additionally, we observed that smoking is associated with greater age-related brain volume loss than observed in morphological studies with healthy individuals (9) and individuals with an alcohol use disorder (24,25). Therefore, we predicted the following: 1) Compared with nonsmokers, smokers demonstrate lower NAA and Glu levels in the DLPFC and ACC and lower NAA concentrations in the frontal, parietal, and temporal lobes; lenticular nuclei; and cerebellar vermis and smokers evidence significantly greater age-related decreases of regional NAA and Glu levels. 2) Smokers show greater levels of risk taking, impulsivity, and poorer decision making. 3) Across smokers and nonsmokers, higher regional NAA and Glu levels are related to better neurocognition, whereas higher NAA and Glu concentrations in DLPFC and ACC are specifically associated with better decision making and with lower risk taking and impulsivity.

METHODS AND MATERIALS

Participants

Healthy, community-dwelling participants were recruited via posters, electronic billboards, and word-of-mouth. Participants were between the ages of 24 and 69 and gainfully employed at the time of the study (Table 1). Before engaging in procedures, 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 Veterans Administration Medical Center. For SVS, there were 35 current smokers (4 smokers were female) and 30 nonsmokers (4 nonsmokers were female); for SI, there were 28 current smokers (2 smokers were female) and 36 nonsmokers (3 nonsmokers were female). The SI data were gathered from 2001–2012, and the SVS data were obtained from 2005–2014. Approximately 50% of participants with SI data also had SVS data; smokers and nonsmokers with both SVS and SI data were equivalent in number. The SI and SVS samples were equivalent on demographic, cigarette use, and alcohol consumption variables.

Table 1. Demographic and Clinical Measures[a]

Variable	Nonsmokers (n = 30)	Smokers (n = 35)
Age (Years)	49.1 ± 12.0	48.6 ± 10.1
Education (Years)	16.5 ± 2.1	14.9 ± 2.1[a]
AMNART	119 ± 9	117 ± 6
Male (%)	87	89
Caucasian (%)	63	71
Body Mass Index	25.5 ± 3.7	26.4 ± 3.8
Beck Depression Inventory	3 ± 3	5 ± 4
STAI Score	31 ± 8	35 ± 9
Average Drinks/Month in 1 Year	14 ± 14	22 ± 20
Average Drinks/Month in Lifetime	19 ± 12	26 ± 20[a]
Biological Mother/Father Positive History of Problem Drinking (%)	28	37
FTND	NA	5 ± 2
Cigarettes/Day	NA	18 ± 6
Total Lifetime Years of Smoking	NA	29 ± 11
Pack-Years	NA	27 ± 15

Data are presented as mean ± SD unless otherwise indicated.

AMNART, American National Adult Reading Test; FTND, Fagerstrom Test for Nicotine Dependence; NA, not applicable; STAI, State-Trait Anxiety Inventory.

[a]$p < .05$.

Complete details of primary inclusion and exclusion criteria are provided elsewhere (26). Briefly, participants were screened for history of neurologic (e.g., seizure disorder, neurodegenerative disorder, traumatic brain injury with loss of consciousness >5 minutes), general medical (e.g., hypertension, diabetes, chronic obstructive pulmonary disease), and psychiatric (i.e., mood, thought, anxiety, substance/alcohol use disorders) conditions or disorders known or suspected to influence neurocognition or brain neurobiology. All female participants were premenopausal, by self-report. Most nonsmoking participants never smoked, although a few smoked <40 cigarettes during their lifetime but had no cigarette or tobacco use in the 10 years before the study. All smoking participants were actively smoking at the time of assessment and smoked at least 10 cigarettes/day for ≥5 years, with no periods of smoking cessation >1 month in the 5 years before study. At the time of the study, no smoker was engaged in any pharmacologic or behavioral smoking cessation program or used any other form of tobacco or electronic cigarettes. All smokers were allowed to smoke ad libitum before all procedures and take smoke breaks when requested.

Psychiatric, Medical, and Substance and Alcohol Consumption Assessment

Participants were administered the screening section of the Structured Clinical Interview for DSM-IV Axis I disorders, Patient Edition, Version 2.0, as well as an in-house questionnaire designed to screen for medical, psychiatric, neurologic, and developmental conditions known or suspected to affect neurocognition or brain neurobiology. Participants also were administered semistructured interviews for lifetime alcohol consumption (lifetime drinking history) and substance use (in-house questionnaire assessing substance type and quantity and frequency of use). From the lifetime drinking history, we derived average number of drinks/month (defined as containing 13.6 g of pure ethanol) over 1 year before enrollment and average number of drinks/month over lifetime. Participants also completed self-report measures of depressive (Beck Depression Inventory) and anxiety (State-Trait Anxiety Inventory, form Y-2) symptoms and family history of problem drinking. Smokers completed a measure of nicotine dependence level (Fagerstrom Test for Nicotine Dependence) and provided information on the total number of cigarettes currently smoked per day and the total number of years of smoking over lifetime. From this information, pack-years—(typical number of cigarettes per day/20) × total number of years of smoking—were calculated for smokers. Before assessment, participants' urine was tested for common illicit substances (e.g., tetrahydrocannabinol, opiates, cocaine, amphetamines), and they were assessed for recent ethanol consumption via breathalyzer. No participant was positive for common illicit substances or ethanol consumption at the time of assessment. Please see (9) for corresponding references for the above measures.

Neurocognitive and Behavioral Assessment

Participants completed a comprehensive battery composed of measures commonly used in clinical and research settings in North America (27). Estimated verbal intelligence was assessed with the American National Adult Reading Test (28). The battery evaluated the following domains of neurocognition reported to be affected adversely by chronic smoking (1,26): cognitive efficiency, executive skills, general intelligence, processing speed, learning and memory (auditory-verbal and visuospatial), visuospatial skills, and working memory. A full description of the neurocognitive battery and results of comparisons of smokers and nonsmokers on the comprehensive neurocognitive battery used in this study are provided elsewhere (26). Participants also completed task-based measures of decision making (Iowa Gambling Task [IGT]) (29) and risk taking (Balloon Analogue Risk Task [BART]) (30,31) and a self-report measure of trait impulsivity (Barratt Impulsiveness Scale-11 [BIS-11]) (32). Scores for all of the aforementioned measures were converted to *Z* scores based on the performance of the nonsmokers in this study. A global neurocognition score was formed via the arithmetic average of *Z* scores for all of the individual domains from the neurocognitive battery.

Magnetic Resonance Acquisition and Processing

MRI. See Supplement 1 Methods for MRI details. The 4T MRI data were acquired on a Bruker MedSpec system (Siemens, Erlangen, Germany); three-dimensional T1-weighted images were obtained with magnetization prepared rapid acquisition gradient-echo imaging, and three-dimensional T2-weighted images via turbo spin echo. The 1.5T MRI data were acquired on a Siemens Vision system (Siemens Medical, Inc., Iselin, New Jersey); magnetization prepared rapid acquisition gradient-echo and T2-weighted double spin echo images were acquired. The 4T structural images were segmented into GM, WM, and cerebrospinal fluid (CSF) using the expectation maximization segmentation method (33) and coaligned with the SVS volumes of interest for determination of their tissue contribution (i.e., GM, WM, CSF) (34). The 1.5T structural images also were segmented into total brain GM, WM, and CSF via expectation maximization segmentation. Subsequently, volumes for the four major lobes and subcortical regions were calculated and coregistered to the expectation maximization segmentation to obtain GM, WM, and CSF fractions for the preceding regions (35). Finally, the segmented 1.5T structural images were coaligned with SI metabolite maps for anatomic localization (e.g., frontal WM) and determination of tissue contributions (i.e., percent GM, WM, CSF) in the corresponding SI voxels (23,36).

Magnetic Resonance Spectroscopy. See Supplement 1 Methods for SVS and SI acquisition and processing details. For SVS at 4T, volumes of interest (VOI) for magnetic resonance spectroscopy were placed over the perigenual ACC and right DLPFC (Figure S1 in Supplement 1). The NAA, Cr, Cho, mI, and Glu signals from both VOI were acquired with a stimulated echo acquisition mode sequence (37), and quantitated metabolite levels were corrected for CSF contribution and scaled to water level from the corresponding VOI.

For SI at 1.5T, spectra were acquired in three 15-mm-thick parallel slices, slice gap of ~6 mm, with a nominal SI voxel size of 1 mL (effective size of 1.5 mL). The SI slices covered the four major cerebral lobes, subcortical nuclei, midbrain, and cerebellar vermis. The reconstructed metabolite maps were coaligned with the segmented structural images, and concentrations (CSF-corrected and scaled to water) were calculated for NAA,

Cho, Cr, and mI. Metabolite concentrations for the left and right hemispheres for all regions were averaged because there were no significant hemispheric differences in either group.

Statistical Analyses

Group Comparisons. Generalized linear modeling compared smokers and nonsmokers on regional metabolite concentrations. The SVS analyses focused on NAA, Cr, Cho, mI, and Glu concentrations in the ACC and DLPFC. The SI analyses focused on NAA, Cr, Cho, and mI levels in the frontal, parietal, and temporal GM and WM; occipital WM; thalami; lenticular nuclei; and cerebellar vermis. Predictors in all models included smoking status (smoker and nonsmoker), age, body mass index, lifetime average drinks/month, GM fraction in the VOI or SI voxel, and smoking status × age interaction. Body mass index was used as a covariate because it was related to metabolite concentrations measured via SVS and SI in healthy controls (38,39). Lifetime average drinks/month was used as a covariate because smokers drank significantly more than nonsmokers. All main effects and interactions were considered statistically significant at $p < .05$. Significant main effects for smoking status were followed-up with t tests (two-tailed) comparing smokers and nonsmokers on mean regional metabolite levels. Despite our a priori predictions for lower regional NAA and Glu in smokers, α levels for all t tests for metabolites in each SVS or SI region were adjusted for multiple comparisons via a modified Bonferroni procedure (40), which accounted for the number of metabolites (five for SVS; four for SI), the number of regions (2 for SVS; 10 for SI), and the moderate-to-strong intercorrelation among metabolites across regions for the entire sample. For SVS, the average intercorrelation among metabolites across the DLPFC and ACC was $r = .46$. For SI, the average intercorrelation of metabolites among the frontal, parietal, and temporal GM and WM, lenticular nuclei, and cerebellum was $r = .66$. Resulting adjusted α levels were $p = .017$ for SVS metabolite t tests and $p = .020$ for SI. Effect sizes for mean metabolite concentration differences between smokers and nonsmokers were calculated with Cohen's d (41).

Decision-Making, Risk-Taking, and Impulsivity Measures. Generalized linear modeling compared smokers and nonsmokers on the IGT net total score; BART average adjusted pumps; and BIS total, attentional, motor, and nonplanning impulsivity scores. Predictors in all models included smoking status (smoker and nonsmoker), age, education, and lifetime average drinks/month. Main effects were considered significant at $p < .05$, and significant main effects for smoking status were followed-up with t tests. The t tests were adjusted for multiple comparisons via the above-mentioned modified Bonferroni procedure, based on the number of individual measures (six) and their average intercorrelation ($r = .44$), resulting in an adjusted α level of $p = .019$. Effect sizes were calculated with Cohen's d.

Associations of SVS and SI Metabolites With Neurocognitive, Risk-Taking, Decision-Making, Impulsivity, and Smoking Severity Measures. Associations of SVS and SI metabolites with neurocognitive, risk-taking, decision-making, and impulsivity measures were examined in the total sample (i.e., smokers and nonsmokers) with linear regression (semipartial correlations reported) controlling for age, education, and lifetime average drinks/month. Relationships of SVS and regional SI metabolite levels with lifetime years of smoking and pack-years were examined in smokers with linear regression (semipartial correlations reported) controlling for age and lifetime average drinks/month. The associations for NAA and Glu were considered significant at $p < .05$, given our a priori predictions; p values for associations of Cho, Cr, and mI with the above-mentioned measures were conservatively adjusted with a standard Bonferroni procedure.

RESULTS

Participant Characteristics

No significant differences were observed between smokers and nonsmokers on age, American National Adult Reading Test, Beck Depression Inventory, State-Trait Anxiety Inventory score, body mass index, and 1-year average drinks/month (all $p > .10$). Groups were equivalent on frequency of Caucasians and positive history of problem drinking in biological parents. Smokers had significantly fewer years of education and more lifetime average drinks/month ($p < .05$) (Table 1).

Group Comparisons of SVS Metabolite Concentrations

ACC. A smoking status × age interaction was observed for Glu [$\chi^2_1 = 8.54$, $p = .003$], where smokers showed lower Glu concentration with increasing age relative to nonsmokers (Figure 1A); a simple slopes difference test for age indicated that the effect of age on Glu level was 1.5 times greater in smokers than in nonsmokers ($p = .003$). Smokers showed trends for lower NAA ($p = .054$) and higher Cho ($p = .052$) compared with nonsmokers. No significant difference in mean Glu, mI, or Cr levels were observed between smokers and nonsmokers (all $p > .15$). For all metabolites except Glu, higher lifetime drinks/month were related to lower levels (all $p < .03$). There was no significant difference of percent GM contributing to the ACC volume between smokers (60%) and nonsmokers (58%).

Right DLPFC. A smoking status × age interaction was yielded for NAA ($\chi^2_1 = 5.88$, $p = .015$) and Glu ($\chi^2_1 = 8.76$, $p = .003$), where smokers showed significantly lower NAA and Glu concentrations with increasing age relative to nonsmokers (Figure 1B); a simple slopes test for age indicated that the effect of age on NAA and Glu in smokers was twice that of nonsmokers (both $p < .015$). Main effects for smoking status were observed for NAA ($\chi^2_1 = 13.69$, $p < .001$), Cr ($\chi^2_1 = 6.85$, $p = .009$), mI ($\chi^2_1 = 11.63$, $p = .001$), and Glu ($\chi^2_1 = 6.81$, $p = .009$); for each metabolite, smokers demonstrated significantly lower concentrations than nonsmokers, and moderate-to-large effect sizes were apparent for these mean differences (Table 2). There was no significant difference in percent GM contributing to the DLPFC volume between smokers (46%) and nonsmokers (43%).

Group Comparisons of SI Metabolite Concentrations

Main effects for smoking status were observed for NAA concentration in the lenticular nuclei ($\chi^2_1 = 8.54$, $p = .003$),

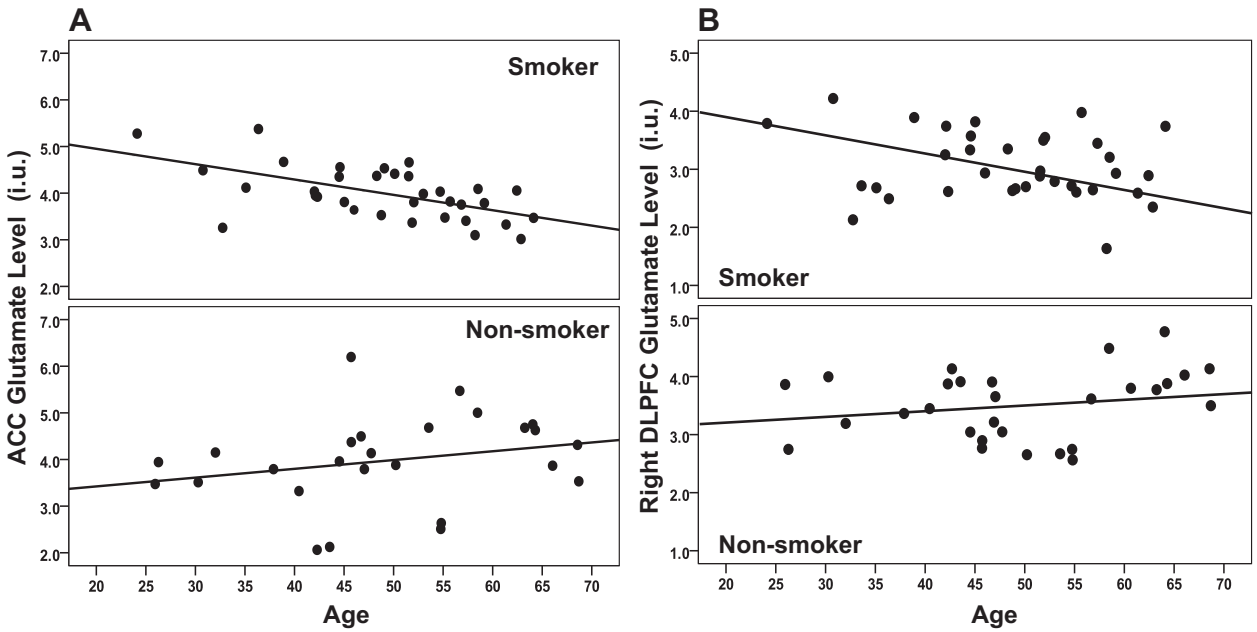

Figure 1. **(A)** Changes in anterior cingulate cortex glutamate levels across age for smokers and nonsmokers. **(B)** Changes in right dorsolateral prefrontal cortex glutamate levels across age for smokers and nonsmokers. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; i.u., institutional units.

with a trend for in the frontal GM ($\chi^2_1 = 4.06$, $p = .041$), where smokers demonstrated significantly lower NAA than nonsmokers in the lenticular nuclei (Table 2). No significant smoking status × age interactions were apparent in any region, and average lifetime drinks/month were not related to metabolite levels in any region (all $p > .20$). No differences were observed between smokers and nonsmokers on SI voxel GM fraction or voxel count in any region (data not shown).

Group Comparisons of Decision-Making, Risk-Taking, and Impulsivity Measures

Smokers demonstrated a lower IGT net total score (indicative of poorer decision making) and higher scores on the BIS motor, nonplanning, and total impulsivity score than nonsmokers (Table 2). No group differences were apparent on the BART average adjusted pumps.

Associations of SVS and SI Metabolite Levels With Neurocognitive, Decision-Making, Risk-Taking, Impulsivity, and Smoking Severity Measures

In the entire cohort (smokers and nonsmokers), there were significant moderate magnitude associations of right DLPFC Glu and NAA concentrations with multiple neurocognitive domain scores as well as with BIS nonplanning impulsivity score; all correlations were in the expected direction (Table 3). Similarly, there were numerous moderate magnitude relationships, in the expected direction, between regional SI NAA levels and neurocognitive domain scores; the SI regions most consistently associated with neurocognition were the frontal GM and lenticular nuclei (Table 3). The direction and magnitude of the above-reported associations was generally consistent for smokers and nonsmokers. No significant associations were apparent for regional metabolite levels with IGT and BART measures (all $p > .20$). In smokers, greater lifetime years of smoking was related to lower Glu in the ACC ($r = -.40$, $p = .012$) and right DLPFC ($r = -.30$, $p = .044$). Smoking severity measures and SI metabolite levels were not significantly related. The pattern and effect sizes for the above-reported findings were essentially unchanged when female participants were excluded from analyses.

DISCUSSION

The primary findings from this study were as follows: 1) Compared with nonsmokers, smokers showed significantly lower NAA, Cr, and mI concentrations in the right DLPFC as well as lower NAA in the lenticular nuclei; smokers also demonstrated significantly greater age-related decreases of NAA in the right DLPFC and of Glu levels in the ACC and right DLPFC relative to nonsmokers. 2) Smokers showed poorer performance on a measure of decision making (IGT) and greater self-reported impulsivity (BIS-11) than nonsmokers. 3) Across the total sample (i.e., smokers and nonsmokers), higher right DLPFC NAA and Glu concentrations as well as NAA in several lobar GM and WM regions and subcortical nuclei, were associated with better performance on multiple neurocognitive domains and lower (nonplanning) impulsivity.

The significantly decreased NAA level in the right DLPFC and lenticular nuclei exhibited by smokers indicates compromised neuronal integrity in these regions (13), and smokers showed notably greater age-related decreases in DLPFC NAA concentration. Smokers also showed notable trends for lower NAA in the ACC ($p = .054$) and the total frontal GM ($p = .041$; as measured with SI), with corresponding moderate effect size (.50–.67). Smokers showed decreased DLPFC Glu level and

Table 2. Group Means for SVS and SI Metabolite Levels (Institutional Units) and Performance on the Iowa Gambling Task and BIS

Variable		Nonsmokers (n = 30)	Smokers (n = 35)	Effect Size (Cohen's d)
SVS Anterior Cingulate Gyrus	NAA	5.88 ± .79	5.49 ± .79	.50
	Cho	1.29 ± .22	1.40 ± .22	.51
	Cr	4.62 ± .75	4.73 ± .74	.14
	mI	3.89 ± .86	3.59 ± .85	.35
	Glu	3.95 ± .69	4.01 ± .69	.09
SVS Dorsolateral Prefrontal Cortex	NAA	5.58 ± .72	4.90 ± .71[a]	.95
	Cho	1.09 ± .17	1.05 ± .18	.22
	Cr	4.59 ± .61	4.18 ± .60[a]	.67
	mI	3.68 ± .66	3.11 ± .66[a]	.87
	Glu	3.45 ± .53	3.09 ± .52[a]	.67
SI Frontal Gray Matter	NAA	33.12 ± 3.09	31.06 ± 3.10	.67
SI Lenticular Nucleus	NAA	29.21 ± 3.52	26.64 ± 3.51[b]	.73
Iowa Gambling Task		−.07 ± .91	−.64 ± .80[c]	.67
BIS Motor Impulsivity		.06 ± 1.05	.86 ± 1.03[c]	.77
BIS Nonplanning Impulsivity		.19 ± 1.07	.91 ± 1.03[c]	.69
BIS Total Score		.20 ± 1.00	.86 ± .98[c]	.66

Data are presented as mean ± SD, values obtained from estimated marginal means.

BIS, Barratt Impulsiveness Scale-11; Cho, choline-containing compounds; Cr, creatine-containing compounds; Glu, glutamate; mI, *myo*-inositol; NAA, *N*-acetylaspartate; SI, spectroscopic imaging; SVS, single volume spectroscopy.

[a]Smokers < nonsmokers, $p \leq .017$.

[b]Smokers < nonsmokers, $p \leq .020$.

[c]Smokers < nonsmokers, $p \leq .019$.

markedly greater age-related reduction in Glu compared with nonsmokers; ACC Glu level did not differ between the groups, but, similar to the DLPFC, smokers demonstrated greater age-related decreases in ACC Glu concentration. These findings indicate that smokers showed the greatest metabolite abnormalities in frontal lobe regions, which complement quantitative MRI studies that found young and middle-aged smokers demonstrated smaller volumes of the ACC, DLPFC (25,42,43), and total frontal GM (25,44).

Nonsmokers demonstrated significantly higher DLPFC mI and Cr, in addition to higher NAA and Glu levels. Elevated cerebral GM mI and Cr have been reported in conditions with pathologically confirmed neuroinflammation [e.g., human immunodeficiency virus infection and Alzheimer's disease (14)]. The synthesis of NAA, mI, Cr, and Glu and the active transport of mI, Cr, and Glu across cell membranes are energetically demanding processes (13,45). Additionally, average intercorrelation of these metabolite levels in the DLPFC of nonsmokers was moderate in magnitude (r = .46). Therefore, the elevated DLPFC mI and Cr concentrations, in conjunction with higher DLPFC NAA and Glu levels, likely reflect the coherence of the mitochondrial function (46,47) of the neuronal and astroglial tissue in this region in nonsmokers. In healthy controls, regional NAA (48) and Glu (15,49) levels show age-related declines across adulthood. The greater age-related reductions in DLPFC NAA and Glu and ACC Glu concentrations demonstrated by smokers suggest that smoking is associated with abnormally accelerated aging effects on the metabolic integrity of tissue in these regions.

Smokers demonstrated a lower IGT total score and a higher BIS-11 total score, which are indicative of poorer decision making and greater impulsivity, respectively. These findings are consistent with previous studies reporting compromised decision making and greater self-reported impulsivity in smokers (50,51).

Across smokers and nonsmokers, higher Glu in the DLPFC and higher NAA in the DLPFC and in several lobar GM and WM regions were associated with better performance on multiple neurocognitive domains. Higher DLPFC NAA and Glu also were related to lower self-reported impulsivity across the study sample. Studies with cognitively normal adults and individuals with various biomedical and psychiatric conditions consistently reported higher regional NAA concentrations were associated with better performance on various neurocognitive measures (13,52,53). Glu is the primary excitatory cerebral neurotransmitter and mediates ~70% of central nervous system synaptic transmission (54). Higher basal ganglia Glu

Table 3. Associations of Regional SVS and SI Derived Metabolites With Neurocognitive, Decision-Making, Risk-Taking, and Impulsivity Measures in the Total Sample (Smokers + Nonsmokers)

Measure	Metabolite	Region	r[a]
Cognitive Efficiency	NAA	Right DLPFC	.28
		Lenticular nuclei	.36
		Temporal WM	.31
	Glu	Right DLPFC	.40
Executive Skills	NAA	Frontal GM	.32
	Glu	Right DLPFC	.30
General Intelligence	Glu	Right DLPFC	.29
Processing Speed	NAA	Lenticular nuclei	.32
	Glu	Right DLPFC	.35
Visuospatial Learning	NAA	Frontal GM	.47
		Temporal WM	.31
		Occipital WM	.36
		Thalamus	.31
		Lenticular nuclei	.38
	Glu	Right DLPFC	.34
Visuospatial Memory	NAA	Frontal GM	.35
		Occipital WM	.33
		Thalamus	.31
		Lenticular nuclei	.38
	Glu	Right DLPFC	.36
Visuospatial Skills	NAA	Right DLPFC	.28
	Glu	Right DLPFC	.33
Global Neurocognition	NAA	Frontal GM	.32
		Lenticular nuclei	.41
	Glu	Right DLPFC	.37
BIS Nonplanning Impulsivity	NAA	Right DLPFC	−.33
	Glu	Right DLPFC	−.36

BIS, Barratt Impulsiveness Scale-11; DLPFC, dorsolateral prefrontal cortex; Glu, glutamate; GM, gray matter; mI, *myo*-inositol; NAA, *N*-acetylaspartate; SI, spectroscopic imaging; SVS, single volume spectroscopy; WM, white matter.

[a]Semipartial correlation coefficient (adjusted for age, education, and lifetime average drinks/month); all reported correlations $p < .05$.

level was correlated with better neurocognitive performance in cognitively normal adults (15,16). The lack of associations between ACC metabolites and neurocognition may be related to the perigenual location of our ACC volume. The perigenual region of the ACC subserves affective/emotional processes, whereas dorsal regions are indicated to be more involved in cognitive processes, such as error monitoring and attentional regulation (55). The ACC and DLPFC subserve multiple cognitive processes, including decision making, risk taking, and impulse control (56,57); the lower DLPFC NAA and Glu and the trends for lower NAA levels in the ACC and total frontal GM in smokers suggest a disturbance in tissue metabolic integrity in those regions, particularly with increasing age, which may partially explain the poorer performance of smokers on the IGT and greater self-reported impulsivity on the BIS-11 as well as the deficient performance on multiple neurocognitive domains observed in this cohort in an earlier study (26). Overall, the findings reinforce the utility of magnetic resonance spectroscopy–derived brain metabolites as practical biomarkers of regional neurobiological integrity and neurocognition. The potential mechanisms by which chronic smoking promotes neurobiological and neurocognitive dysfunction are reviewed elsewhere (1,11).

This study has limitations that may affect the generalizability of the findings. Unrecorded premorbid/comorbid group differences in lifestyle or biomedical conditions (e.g., diet/nutrition, exercise, subclinical pulmonary or cardiovascular dysfunction) and genetic polymorphisms (58) may have influenced the results. The small number of female participants precluded assessment for sex effects.

In conclusion, this study contributes novel information to the expanding body of evidence that cigarette smoking in young and middle-aged individuals is associated with significant age-related neurobiological abnormalities, particularly in anterior frontal regions implicated in the development and maintenance of addictive disorders. Longitudinal studies on the effects of smoking cessation on the regional brain metabolites measured in this study, with a greater number of female participants, are warranted to determine if the observed metabolite abnormalities are persistent or normalize with smoking cessation.

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TCD was responsible for the study design, 4T data acquisition and processing, neuropsychological assessments, all statistical analyses, data interpretation, and manuscript preparation. SG and AM acquired and CA processed 1.5T data under supervision of DJM. DEM acquired and processed 4T data under supervision of DJM. All authors made significant contributions to the content and editing of the manuscript.

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