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Nicotine Abstinence-induced Cerebral Blood Flow Changes by Genotype

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Abstract

This study explored whether functional genetic variants previously associated with nicotine dependence are associated with regional cerebral blood flow (rCBF) changes during nicotine abstinence (compared to satiety; smoking as usual). Thirteen smokers participating in a prior arterial spin labeled (ASL) perfusion MRI study were scanned on two occasions (after >12 hours abstinence vs. satiety) [24], and were genotyped for variants in the dopamine D2 receptor (*DRD2*-141 Ins/DelC; *DRD2* C957T); a dopamine metabolizing enzyme (*COMT* val/val), and the mu opioid receptor (*OPRM1* A118G). Significantly greater CBF increases were found in regions previously linked with cigarette cravings among carriers of the DelC variant of *DRD2*-141 and among the *COMT* val/val group. Smokers with TT genotypes for the *DRD2* C957T exhibited less change in rCBF in abstinence relative to satiety, compared to those with CC or CT genotypes. Finally, smokers with *OPRM1* AA genotypes showed significant increases in CBF in regions associated previously with cigarette cravings. While preliminary, these results suggest a neural mechanism through which these genetic variants may be linked with nicotine dependence, and provide further support for increased biological vulnerability in these subgroups of smokers.

Keywords

perfusion MRI; nicotine; addiction; genetics

Introduction

Nicotine dependence is a highly heritable trait which has been linked to polymorphisms in genes in the dopamine, endogenous opioid, and other brain reward pathways [13]. Emerging

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Conflicts of Interest: John A. Detre is an inventor of ASL perfusion MRI and has received royalties from the University of Pennsylvania for its licensure.

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data also support genetic associations with intermediate components, or “endophenotypes” of nicotine dependence, including nicotine reward [19], cue-induced cigarette craving [11], and abstinence symptoms [8]. Genetic variants associated with reduced dopaminergic tone have also been linked with greater smoking-induced dopamine release [3], nicotine-induced reductions in verbal working memory and processing efficiency [12], and BOLD signal to smoking cues [16].

We reported recently that abstinence-induced urges to smoke correlate significantly with regional cerebral blood flow (rCBF) changes during abstinence (vs. satiety; smoking as usual) in regions involved in drug reward, behavioral control, emotion and memory [24]. Because of the tight coupling between changes in rCBF and neural metabolism, rCBF provides a measure of regional brain function [18]. In this paper, we explored whether abstinence-induced increases in rCBF are greater among smokers with genotypes that may relate to reduced dopaminergic tone or altered mu opioid receptor function. Based on in-vitro data, these include: alleles associated with reduced dopamine D2 receptor (*DRD2*) transcriptional efficiency (*DRD2* -141 DelC) [1], decreased *DRD2* mRNA stability [6] and D2 receptor binding potential [10] (*DRD2* 957T), decreased prefrontal cortex (PFC) dopamine levels (Catechol-O-Methyltransferase (*COMT* Val158) [4], and increased mu opioid receptor mRNA and protein (*OPRM1* A118) [26]. Each of these genotypes has also been associated with smoking cessation in prior research [13].

Material and Methods

Procedures were approved by the University of Pennsylvania Institutional Review Board. Eligibility criteria and procedures have been described previously [24]. Participants were fifteen adult smokers (> 10 cigarettes per day) recruited through advertisements. They were required to abstain from psychotropic medications for 14 days prior to and throughout the study, and to refrain from alcohol or other drugs for ≥ 24 hrs. prior to each session.

In a within-subject design, smokers participated in 2 imaging sessions occurring 1–3 weeks apart: 1) smoking as usual (satiety) and 2) overnight (12–14 hours) abstinent (order counterbalanced). For the smoking session, participants smoked one of their own brand cigarettes prior to entering the clinic; carbon monoxide (CO) level was controlled in the analyses. Including set-up time, there was about 45–60 minutes between the last cigarette smoked (on the smoking as usual day) and the imaging session. The abstinent session required a CO level <15ppm.

As described previously [24], ASL perfusion MRI was performed on a Siemens 3T Trio MR scanner (Siemens AG, Erlangen, Germany) using a product volume coil. ASL perfusion MRI provides a noninvasive way to quantify CBF during a task condition or a resting state using magnetically labeled arterial blood water as an endogenous tracer [5]. Its perfusion measurements are highly reproducible across intervals varying from a few minutes to 7 weeks [9,17] and are associated with cigarette craving among smokers [24].

High resolution structural MR images were acquired in both sessions for CBF image spatial normalization, using a T1-weighted 3D MPRAGE sequence with 160 slices, 1.0 mm thickness, 22cm field-of-view (FOV), 192×256 matrix, TI/TR/TE=1100/1630/3 ms, Nex=1. Immediately after MPRAGE scan, 40 resting label/control image pairs were acquired to measure CBF using an amplitude modulated continuous ASL perfusion MRI sequence with parameters of: labeling time =2 sec, post-labeling delay = 1200 ms, field-of-view =22cm, matrix=64×64×16, flip angle=90°, TR=4 sec, TE=17 msec, slice thickness 7 mm, inter-slice spacing of 0.5 mm. During the perfusion scan, participants were instructed to lie quietly in the scanner and were reminded not to fall asleep.

Genotyping was performed using Assays-on-Demand SNP genotyping reagents and the genotypes were called utilizing the Allelic Discrimination End-point Analysis on the ABI Prism 7900 HT Sequence Detection System (Applied Biosystems, Foster City, CA). For each of the analyses, the hypothesized high risk group was coded as 1 and is underlined: *DRD2*-141C (DelC/InsC (n=4) vs. InsC/InsC (n=9); *DRD2* C957T (TT (n=6) vs. CC or CT (n=7)); *COMT* (val/val (n=3) vs. val/met or met/met (n=7)); *OPRM1* (AA (n=10) vs. AG or GG (n=3)). All genotypes were in Hardy-Weinberg equilibrium.

Images were preprocessed with an SPM5 (Wellcome Department of Cognitive Neurology, London, UK) based ASL data processing toolbox, ASLTbx [23] to get the spatially normalized CBF maps. One subject was excluded due to excessive motion, and genotype data were unavailable for another, resulting in a sample size of 13. Contrast analysis between the abstinence and smoking session was then conducted on each subject's normalized CBF images using a general linear model (GLM) provided in SPM5. Regions-of-interest (ROIs) and whole brain data exploratory analysis were then performed to assess the associations of genetic variation with the abstinence-induced CBF changes (abstinence minus satiety). A priori ROIs were defined in the dorsolateral prefrontal cortex (DLPFC) and ventral striatum (VS). The former was chosen because *COMT* activity in DLPFC plays a critical role in regulating the dopamine activity [22]. The VS was chosen to assess the effects of the *OPRM1*A118G, *DRD2* -141C, and *DRD2* C957T variants because this region has the highest density of these two receptors. DLPFC was defined using the Pickatlas utility [15]; and the VS was defined manually as in the literature [21]. Multiple regressions were then performed with the ROI data as dependent variable, and genotype data as independent variables. Age and gender were included as nuisance covariates. The same steps were then performed at each voxel of the CBF map in the exploratory whole brain analysis. Based on the sample size, the exploratory analysis results were first thresholded with an uncorrected voxelwise threshold of $P < 0.005$ ($t = 3.25$). Multiple comparison corrections were then performed using the family-wise-error (FWE) theory or the false detection rate (FDR) based correction method [7] with or without the small volume correction (SVC) [25]. The small volume was chosen using a sphere located in the center of the corresponding region.

Results

Of the 13 participants with usable data, 6 were male and 7 were female, the mean age was 38.3 (SD=2.9), they smoked on average, 16.9 (SD=5.6) cigarettes/day, and had an average score of 4.77 (SD=0.57) on the Fagerstrom Test for Nicotine Dependence. All were of European ancestry. As reported previously [24], the nicotine abstinence manipulation produced significant differences in cravings across the two sessions (average craving scores of 3.38 (SD=0.56) vs. 0.77 (SD=0.26) for abstinence and smoking respectively; paired t-test, $P < .0005$).

ROI based analysis

In the ROI-based analysis, there was a nonsignificant trend for an association of *COMT* genotype with CBF change in DLPFC (abstinence minus satiety), with greater increases in the val/val group ($P = 0.079$). For the VS ROI, there was a nonsignificant trend for *DRD2* C957T ($P = .063$), with the CT/CC group exhibiting greater increases (abstinence minus satiety) than the TT group.

Whole brain analysis

With a voxelwise threshold of $P < 0.005$ (uncorrected for multiple voxels) and cluster size over 30, brain regions showing differences the rCBF increase (abstinence minus satiety) between different genotype groups are illustrated in Figures 1 – 4, and are summarized in Table 1. In all figures, the Z (or X) value above each image indicates the slice location along the z (inferior

to superior direction) (or x (left to right direction)) axis in the MNI space (MNI space refers to the Montreal Neurological Institute (MNI) standard brain space, which is widely used in fMRI field).

As shown in Figure 1 and Table 1, greater rCBF increases (abstinence minus satiety) were found in carriers of the *DRD2*-141 DelC allele compared to those homozygous for the InsC allele. The statistical parametric map was first thresholded with an uncorrected voxelwise $P < 0.005$ and cluster size > 30 . With cluster level FWE correction, a significant perfusion change difference cluster (cluster level $P = 0.023$, FWE correction) was found in the right dorsolateral prefrontal cortex (DLPFC). With SVC, significant differences were also found in the prefrontal cortex (PFC) ($P = 0.022$ FDR with SVC, $r = 15$ mm), the right orbitofrontal cortex (OFC)/PFC ($P = 0.008$ FDR with SVC, $r = 15$ mm), the left parietal cortex ($P = 0.045$ FDR with SVC, $r = 15$ mm), right inferior frontal cortex (IFC) ($P = 0.035$ FDR with SVC, $r = 15$ mm), left OFC ($P = 0.032$, FDR, $r = 10$ mm), and right striatum ($P = 0.039$ FDR with SVC, $r = 12$ mm).

The comparison of rCBF increases (abstinence minus satiety) between homozygous carriers of the *DRD2* 957T allele (TT group) and the CC/CT group are summarized in Figure 2 and Table 1 (note: for all comparisons, rCBF change was reduced for the TT group). At a voxelwise uncorrected threshold of $P < 0.005$ and cluster size over 30, significant differences were found using SVC in the left insula/putamen ($P = 0.034$, FDR, $r = 12$ mm), left OFC ($P = 0.042$, FDR, $r = 10$ mm), left thalamus ($P = 0.049$, FDR, $r = 12$ mm), the ventral striatum ($P = 0.024$, FDR, $r = 10$ mm), and the left fusiform ($P = 0.031$, FDR, $r = 12$ mm).

Figure 3 and Table 1 show the regions of rCBF increases (abstinence minus satiety) which were significantly different in the *COMT* val/val group compared to met allele carriers (note: for all comparisons rCBF change was greater for val/val group). With the uncorrected voxelwise threshold of $P < 0.005$ and cluster size over 30, significant differences were found using SVC in the left DLPFC ($P = 0.048$, FDR, $r = 14$ mm) and the superior frontal cortex ($P = 0.039$, FDR, $r = 12$ mm).

Figure 4 and Table 1 show the regions of rCBF increases which were significantly different between the *OPRM1* AA group and the AG/GG group (note: for all comparisons, rCBF change was greater for AA group). Significant rCBF change differences using voxelwise statistical threshold of $P < 0.05$ (FDR correction) were found in the striatum/thalamus, left inferior temporal cortex (ITC), and the right superior temporal cortex. At the uncorrected voxelwise threshold of $P < 0.005$ with SVC, significant differences were found in the PFC ($P = 0.01$, FDR, $r = 12$ mm), medial OFC ($P = 0.021$, FDR, $r = 12$ mm), right insula ($P = 0.022$, FDR, $r = 12$ mm), and the posterior cingulate cortex (PCC) ($P = 0.046$, FDR, $r = 12$ mm).

Discussion

The present study provides preliminary data supporting genetic associations with regional brain function during nicotine abstinence versus satiety in chronic smokers. We hypothesized that abstinence-induced increases in rCBF that have been associated previously with smoking urges [24] would be greater among smokers with genotypes that relate to reduced dopaminergic tone or altered mu opioid receptor function. These include alleles associated with decreased *DRD2* transcriptional efficiency (*DRD2*-141 DelC group) [1], decreased *DRD2* mRNA stability [6] and binding potential [10] (*DRD2* C957T TT group), decreased PFC dopamine (*COMT* val/val group) [4], and increased mu opioid receptor mRNA (*OPRM1* AA group) [26]. These hypotheses were supported, except for the *DRD2* C957T TT group, for which we observed significantly less rCBF change. The ROI based analysis also demonstrated trends toward differences between genotype groups in the DLPFC (for *COMT* genotype) and VS (for

DRD2 C957T genotype), regions where the apparent contribution of these polymorphisms should be greater.

In the whole brain data based exploratory analysis, regions of interest showing rCBF differences (abstinence minus satiety) for the hypothesized high risk groups include those correlated with nicotine withdrawal symptoms [20,21,24] as well as cue-induced craving [2], such as DLPFC, IFC, OFC, insula, ventral striatum, thalamus, parietal cortex and PCC. Our data are generally consistent with those of Brody and colleagues [3], who reported that genetic variants associated with reduced dopaminergic tone are associated with increased dopamine D2 receptor binding following smoking. Evidence for increased activation in the *OPRM1* AA group in abstinence versus satiety is also consistent with increased nicotine reward and relapse risk among these smokers in clinical studies [14,19].

These results must be considered preliminary and hypothesis-generating, due to the small sample sizes. Also, since analyses of measures with a single assessment (i.e., withdrawal, craving) are less powerful than imaging data that incorporate repeated measures, we did not find significant differences in these self-report outcomes by genotype.

In summary, the present findings provide new insights about the neural mechanisms that may link genetic susceptibility variants to nicotine dependence. Future larger studies adequately powered to test associations of genotype and rCBF change with clinical endpoints are needed to determine the clinical significance of these findings.

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Figure 1.

Genotype differences in nicotine abstinence-induced CBF changes (delta rCBF) between the *DRD2*-141 DelC/InsC subgroup vs. Ins/Ins group. Hot color means greater in the DelC/InsC subgroup. The color bar indicates the range of t-values displayed. Spatial location of each slice is indicated by the number in the upper left corner of the slice image and is marked by the horizontal lines overlaid on the sagittal slice in the bottom row.

Figure 2.

Genotype differences in nicotine abstinence-induced rCBF changes (delta rCBF) between the *DRD2* C957T TT and the CT/CC group. Cool color means less rCBF difference in the TT group. The color bar indicates the range of t-values displayed. Spatial location of each slice is indicated by the number in the upper left corner of the slice image and is marked by the horizontal lines overlaid on the sagittal slice in the bottom row.

Figure 3.

Genotype differences in nicotine abstinence-induced rCBF changes (delta rCBF) between the *COMT* val/val subgroup and the val/met+met/met group. Hot color means greater in the val/val subgroup. The color bar indicates the range of t-values displayed. Spatial location of each slice was indicated by the number in the upper left corner of the slice image and is labeled by the white lines overlapped on the right bottom sagittal slice.

Figure 4.

Genetic differences in nicotine abstinence-induced rCBF changes (delta rCBF) between the *OPRM1* AA vs. the AG/GG group. Hot color means greater in the AA subgroup. The color bar indicates the range of t-values displayed. Spatial location of each slice is indicated by the number in the upper left corner of the slice image and also be labeled by the white lines (for axial slices) and the green lines (for the sagittal slices).

Table 1

Brain regions showing significant genetic effects of the abstinence-induced perfusion changes. The location of the peak t within each region is given by the MNI coordinate. The P value refers to the one with SVC based FDR correction if not explicitly mentioned otherwise.

Comparison	Region	Peak t-value	x	y	z	P value	SVC r(mm)
DRD2-141 Del<InsC	rDLPFC	6.59	48	40	20	0.023 cluster level, FWE correction	15
	PFC	5.51	12	58	34	0.022	15
	OFC/PFC	7.92	36	56	-8	0.008	15
	IParietal	4.78	-40	-48	50	0.045	15
	rIFC	4.85	52	20	6	0.035	15
	IOFC	4.01	-28	38	-12	0.032	10
DRD2-957 TT<CC/CT	rStriatum	4.05	20	18	0	0.039	12
	Insula/putamen	4.92	-38	12	10	0.034	12
	IOFC	4.62	-32	32	-18	0.042	10
	thalamus	3.56	-16	-22	12	0.047	12
	VS	5.79	4	16	-8	0.025	10
	IFusiform	4.15	-26	-50	-4	0.027	12
COMT Val/Val> Val/met+met/met	IDL PFC	4.12	-44	4	38	0.049	15
	SFC	3.99	2	-4	58	0.039	12
OPRM1 AA>AG/GG	Striatum/thalamus	9.55	14	-10	-6	0.047 voxelwise FDR correction	12
	lITC	9.38	-30	2	-34		12
	rSTC	8.65	54	-4	-9		12
	PFC	5.39	8	48	26	0.01	12
	mOFC	5.52	10	40	-10	0.021	12
	rInsula	5.07	36	8	-13	0.22	12
	PCC	4.11	6	-48	24	0.046	12

Abbreviations: rDLPFC right dorsolateral prefrontal cortex, PFC prefrontal cortex, OFC orbitofrontal cortex, l left, IFC inferior frontal cortex, VS ventral striatum, SFC superior frontal cortex, ITC inferior temporal cortex, STC superior template cortex, PCC posterior cingulate cortex.