

Smoking, Dopamine Transporter, and Hand Tremor

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Aim: The purpose of the study was to evaluate the relationship between the number of packs smoked per day and specific uptake ratio (SUR) in the striatum on Tc-99m TRODAT, and frequency of hand tremor.

Methods: It was a prospective, cross-sectional study. In all, 23 healthy nonsmokers and 37 current smokers were recruited in the study. All subjects underwent Tc-99m TRODAT SPECT, brain CT scan, thyroid function test, tremor measurement system, and neurologic examinations.

Results: There were significant differences in the SUR in the striatum on Tc-99m TRODAT and in the frequency of hand tremor in rest state and in arm extended state among nonsmokers (grade I), current smokers with less than 1 pack smoked per day (grade II), and current smokers with equal or more than 1 pack smoked per day (grade III) by ANOVA (all $P < 0.001$). After adjusting for age and gender, there was a significantly negative correlation between smoke grade and SUR in the striatum on Tc-99m TRODAT by multiple linear regression ($\beta = -0.45$, $P < 0.001$). Smoke grade was the significant predictor for the frequency of hand tremor in rest state and in arm extended state, after adjusting for age and gender by multiple linear regression ($\beta = 14.70$, $P < 0.001$; $\beta = 15.37$, $P < 0.001$).

Conclusions: There is a dose-response relationship between the number of packs smoked per day and SUR in the striatum, and the frequency of hand tremor. Decreased dopamine transporter binding in the striatum and increased frequency of hand tremor in smokers may have important implications for evaluating the impact of smoking on the central and peripheral nerve systems.

Key Words: smoke, Tc-99m TRODAT, dopamine transporter, hand tremor

(*Clin Nucl Med* 2012;37: 35–38)

Cigarette smoking increases the risk of numerous health problems, including malignancies, coronary artery disease, and pulmonary disorder. According to the World Health Organization, tobacco smoking is responsible for the death of around 5 million people each year.^{1–3} Cigarette smoke is composed of thousands of chemical compounds including nicotine, the addictive substance of cigarettes, carbon monoxide, and polycyclic aromatic hydrocarbons. It is well established that the dopaminergic system is a target site of nicotine.⁴

Dopamine transporters (DAT) mediate the reuptake of free dopamine from the synaptic cleft back into the axonal button.⁵ Tc-99m [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]

methyl](2-mercaptoethyl)amino]ethyl]amino]ethanethiolato(3-)-N₂,N₂',S₂,S₂']oxo-[1R-(exo-exo)] (TRODAT) is an agent for dopamine transporters that measures dopamine innervation of the striatum. Tc-99m TRODAT is a Tc-99m-labeled tropane derivative that is located only on dopaminergic nerve terminals. Postmortem studies have demonstrated a close relationship between DAT concentrations and striatal dopamine levels. Therefore, DAT imaging provides a measure of dopamine terminal innervation of the striatum.^{6–8}

DAT is also the target of several “DAT-blockers,” including amphetamines and cocaine. Krause et al found that smokers with attention deficit hyperactivity disorder (ADHD) have reduced DAT compared with nonsmokers with ADHD, therefore, they suggested that nicotine acts in a similar way on striatal DAT as do stimulants, reducing primarily elevated DAT density in adults with ADHD.⁹ The study has indicated that certain components of cigarette smoke can inhibit the activity of both A and B isoforms of monoamine oxidases (MAOs) enzyme in the basal ganglia.¹⁰ MAO is known to breakdown dopamine.¹¹ Decreased MAO A and B are likely to result in greater dopamine levels and lower DAT availabilities.

Occasionally, we noticed hands tremor in smokers in clinics. It has been reported that tobacco smoking increased tremor.^{12–14} Some studies reported an inverse association between smoking and Parkinson disease (PD).^{15–17} We are interested in differentiating the hand tremor in smokers from that in Parkinsonism.

The purpose of the study is to evaluate the relationship between the number of packs smoked per day and specific uptake ratio (SUR) in the striatum on Tc-99m TRODAT, and frequency of hand tremor.

MATERIALS AND METHODS

Subjects

It was a prospective, cross-sectional study. In all, 23 healthy nonsmokers and 37 healthy current smokers were prospectively recruited in the study. None of the study subjects had a history of physical, psychiatric, neurologic, cognitive, severe central nerve systemic, degenerative disease, or severe head trauma with loss of consciousness. All subjects underwent Tc-99m TRODAT SPECT, brain CT scan, thyroid function test, tremor measurement system, and neurologic examinations. The demographic information and the number of packs smoked per day were recorded.

SUR in the striatum on Tc-99m TRODAT SPECT was calculated in all subjects. A neurologist performed a detailed neurologic examination on all subjects while focusing on abnormal movements such as tremors, coordination, and cognitive function.

The Ethical Committee for Human Research at the Show Chwan Memorial Hospital approved the study protocol. Informed consent was obtained from all subjects before study initiation.

Frequency of Hand Tremor Measurement

Tremor Measurement System and software version 3.02 (Neuro-Test Inc., Pasadena, CA) were used to measure the frequency of hand tremor. The test lasts for 1 minute and consists of two 30-second parts: hand tremor in the rest state (subject sits with arm relaxed at his/her side) and hand tremor in the arm extended state (same position but arm outstretched in front of his/her level

Received for publication March 2, 2011; revision accepted August 27, 2011.

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Conflicts of interest and sources of funding: none declared.

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ISSN: 0363-9762/12/3701-0035

with shoulder and fingers relaxed pointing toward the floor). The larger detector is held between the thumb and fingers of the dominant arm. The tiny measurement device of $1 \times 1 \times 0.4 \text{ cm}^3$ is taped to the proximal phalange of the third finger with the dominant arm out stretched and the finger passively flexed. Frequency of tremor movements per second (hertz, Hz) was recorded.

Tc-99m TRODAT SPECT Protocol and Interpretation

Human smokers expose themselves to nicotine and cigarette smoke chronically; therefore, we evaluated the chronic effects of smoking on DT in this study. The elimination half-life of nicotine in the body is 2 hours.¹⁸ The subjects were asked not to smoke on the examination day. The time interval between the last cigarette smoking and TRODAT imaging was 10 to 12 hours.

A dual-head gamma camera, Sophia DXT-XLi (GE/SMV, Versailles, France), was used with a low-energy/high-resolution collimator. The photon attenuation correction was performed using Chang's first-order method with a broad-beam attenuation coefficient of 0.12 cm^{-1} , and 128×128 image with a pixel size of $2.11 \times 2.11 \text{ mm}^2$ was reconstructed using the filtered back-projection algorithm with a Metz filter (order 3.5, cutoff 7 cm^{-1}). The thickness of the reconstructed image was 2.9 mm. The brain SPECT images were acquired 3 hours after injecting 740 MBq (20 mCi) Tc-99m TRODAT. Regions of interest were marked for one side of the striatum in reference to the corresponding computed tomography scan and were fitted to the contralateral side. Regions of interest were drawn over the whole striatum on composite images of the 3 slices with the highest basal ganglia activity. The occipital cortices (OCs) were also drawn in the same way and served as background areas.

The value of SUR was calculated by subtracting the mean counts per pixel in the OC from the mean counts per pixel in the whole striatum and dividing the result by the mean counts per pixel in the background. The formula for the SUR in the striatum is $(\text{striatum} - \text{OC})/\text{OC}$.

Smoke Grade

All subjects were graded by the number of packs smoked per day. Nonsmokers were defined as grade I group, current smokers with less than 1 pack smoked per day were defined as grade II group, and current smokers with equal or more than 1 pack smoked per day were defined as grade III group.

Statistical Analysis

The mean values of SUR in the striatum on Tc-99m TRODAT and in the frequency of hand tremor in rest state and in arm extended state among 3 smoke grade groups were compared by ANOVA. The relationship between smoke grade and SUR in the striatum on Tc-99m TRODAT SPECT, and between frequency of hand tremor in rest state and in arm extended state were analyzed by Pearson correlations and multiple linear regression, after adjusting for possible covariates.

All statistical analyses were performed on a personal computer using the statistical package SPSS for Windows (Version 13.0). A *P* value of 0.05 was considered to represent statistical significance.

RESULTS

There were 8 male and 15 female healthy nonsmokers (grade I) (mean age, 40.43 ± 11.22 years), 11 male and 9 female

TABLE 1. The Definition of Smoke Grade, Demographic Information, Specific Uptake Ratio (SUR) on Tc-99m TRODAT SPECT, and Frequency of Hand Tremor in 3 Smoke Grade Groups

Smoke Grade	Grade I	Grade II	Grade III	<i>P</i>
Definition	Nonsmokers	Current smokers with less than 1 pack smoked per day	Current smokers with equal or more than 1 pack smoked per day	
No.	23	20	17	
Age (y)	40.43 ± 11.22	33.35 ± 7.60	38.65 ± 8.67	
Gender (male, female)	8 vs. 15	11 vs. 9	11 vs. 6	
SUR in the striatum	2.03 ± 0.44	1.42 ± 0.07	1.12 ± 0.07	<0.001
Frequency of hand tremor in rest state (hertz)	5.76 ± 0.50	18.76 ± 0.89	35.32 ± 0.72	<0.001
Frequency of hand tremor in arm extended state (hertz)	9.71 ± 0.57	22.80 ± 1.12	40.78 ± 1.88	<0.001

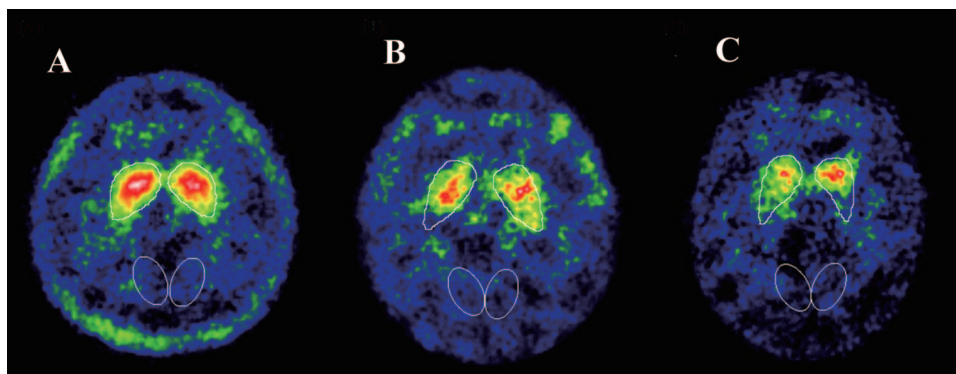


FIGURE 1. Tc-99m TRODAT SPECT of healthy nonsmoker (grade I) (A), current smoker with less than 1 pack smoked per day (grade II) (B), and current smokers with equal or more than 1 pack smoked per day (grade III) (C).

current smokers who smoked less than 1 pack smoked per day (grade II) (mean age, 33.35 ± 7.60 years), and 11 male and 6 female current smokers who smoked equal or more than 1 pack smoked per day (grade III) (mean age, 38.65 ± 8.67 years) in this study. The mean values of SUR in the striatum on Tc-99m TRODAT among grade I, grade II, and grade III groups were 2.03 ± 0.44 , 1.42 ± 0.07 , and 1.12 ± 0.07 , respectively. The mean frequency of hand tremor in rest state in grade I, grade II, and grade III groups was 5.76 ± 0.50 (Hz), 18.76 ± 0.89 (Hz), and 35.32 ± 0.72 (Hz), respectively. The mean frequency of hand tremor in arm extended state in grade I, grade II, and grade III groups was 9.71 ± 1.12 (Hz), 22.80 ± 1.12 (Hz), and 40.78 ± 1.88 (Hz), respectively. There were significant differences in the SUR in the striatum on Tc-99m TRODAT and in the frequency of hand tremor in rest state and in arm extended state among 3 groups by ANOVA (all $P < 0.001$) (Table 1).

There was homogenous distribution of radioactivity in the striatum in grade I group (Fig. 1A), moderately decreased tracer uptake in the striatum in grade II group (Fig. 1B), and severely decreased tracer uptake in the grade III group (Fig. 1C).

A neurologist performed a detailed neurologic examination on all subjects while focusing on abnormal movements such as tremors, coordination, and cognitive function. No definitively abnormal clinical signs were identified. All subjects had normal thyroid function test.

There was a significantly negative correlation between smoke grade and SUR in the striatum on Tc-99m TRODAT SPECT by Pearson correlations ($r = -0.80$, $P < 0.001$). There was a significantly positive correlation between smoke grade and the frequency of hand tremor in rest state, and between smoke grade and the frequency of hand tremor in arm extended state by Pearson correlations ($r = 0.93$, $P < 0.001$; $r = 0.92$, $P < 0.001$) (Table 2) (Fig. 2).

TABLE 2. The Relationship Between Smoke Grade and Specific Uptake Ratio (SUR) in the Striatum on Tc-99m TRODAT, and Frequency of Hand Tremor by Pearson Correlation

	Smoke Grade	P
SUR in the striatum	$r = -0.80$	$P < 0.001$
Frequency of hand tremor in rest state (hertz)	$r = 0.93$	$P < 0.001$
Frequency of hand tremor in arm extended state (hertz)	$r = 0.92$	$P < 0.001$

After adjusting for age and gender, there was a significantly negative correlation between smoke grade and SUR in the striatum on Tc-99m TRODAT by multiple linear regression ($\beta = -0.45$, $P < 0.001$). Smoke grade was the significant predictor for the frequency of hand tremor in rest state and in arm extended state, after adjusting for age and gender by multiple linear regression ($\beta = 14.70$, $P < 0.001$; $\beta = 15.37$, $P < 0.001$) (Table 3).

DISCUSSION

In this study, we found decreased radioactivity in the striatum on Tc-99m TRODAT SPECT in current smokers. There was a dose-response relationship between number of packs smoked per day and the SUR in the striatum on Tc-99m TRODAT, and the frequency of hand tremor.

It has been reported in the scientific literature that there were decreases in DAT binding in smokers.^{19,20} Salokangas et al reported that presynaptic DA activity is higher in smokers by using PET with F-18 DOPA as the ligand.²¹ The studies reported that nicotine stimulates DA release.^{22,23}

The stimulants are known as the “DAT-blockers.” These chemicals increase the concentration of DA in the synaptic gap and inhibit the action of DAT. Krause et al suggested that nicotine acts in a similar way on striatal DAT as do stimulants, reducing primarily elevated DAT density in adults with ADHD.⁹ Some studies found that smoking has been shown to inhibit MAO activity.^{11,24,25} Leroy et al confirmed an inhibition of MAO-A in caudate and thalamus in smokers by [C-11]befloxatone PET scan.²⁶ MAO is known to breakdown DA, so decreased MAO is likely to result in greater DA levels.

Based on the results of this study, we hypothesize that the impact of cigarette smoking may mimic the impact of the stimulants on striatal DAT, increasing dopamine levels in the synaptic gap and inhibiting the action of DAT. In this study, we confirmed that smoking reduced DAT activity in smokers. We also hypothesize that TRODAT uptake competes with intrinsic greater DA levels by nicotine effects of smoking and results in lower DAT availabilities. Thus, we did not suggest that there was nigrostriatal degeneration in smokers. Our hypotheses may provide the reasons for the inverse association between smoking and PD reported by the studies.^{15–17} It has been reported that DAT blockade may play a role in the rewarding influence of addictive behaviors.²⁷ The hypotheses of the impact of smoking on DA levels, DAT, and MAO in the striatum need more researches to confirm it.

It is known that tobacco smoking increased tremor. Smoking-related tremor is thought to be mediated by nicotine-induced catecholamine release. Nicotine is believed to act by binding the nico-

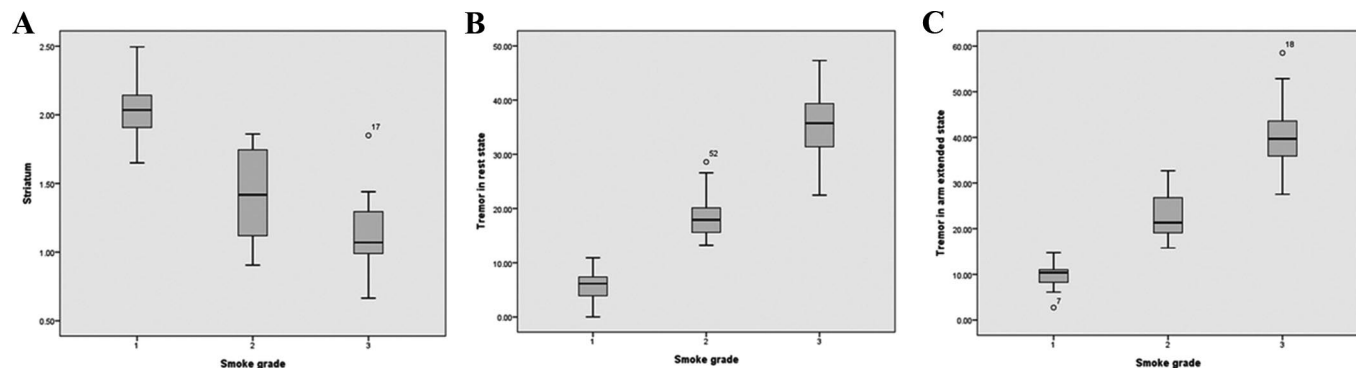


FIGURE 2. Boxplots of specific uptake ratio (SUR) in the striatum on Tc-99m TRODAT (A), the frequency of hand tremor in rest state (B), and the frequency of hand tremor in arm extended state (C) in 3 smoke grade groups.

TABLE 3. The Correlation Between Smoke Grade and Specific Uptake Ratio (SUR) in the Striatum on Tc-99m TRODAT SPECT, Frequency of Hand Tremor in the Rest State and Arm Extended State After Adjusting for Age and Gender by Multiple Linear Regression

Variables	Beta Coefficients	P
Dependent variable: SUR in the striatum		
Age	-0.004	0.35
Sex	-0.10	0.21
Smoke Grade	-0.45	<0.001*
Dependent variable: frequency of hand tremor in the rest state		
Age	0.06	0.34
Sex	0.46	0.72
Smoke Grade	14.70	<0.001*
Dependent variable: frequency of hand tremor in the arm extended state		
Age	0.09	0.22
Sex	1.00	0.49
Smoke Grade	15.37	<0.001*

*P < 0.05.

tinic cholinergic receptors in skeleton muscle.¹²⁻¹⁴ This study was not designed to capture the acute effects of smoking; tremor was not measured in smokers immediately after they smoked a cigarette. The interest of our study was the nonacute effects of smoking on the frequency of hand tremor. In this study, we found that hand tremor in smokers was the high-frequency tremor. Hand tremor in smokers is different from the rest tremor in PD, low-frequency tremor (4–6 Hz).²⁸ The findings of this study may imply that the mechanism of hand tremor in smokers is distinct from PD.

There were potential limitations in this study. First, smoking was assessed by self-report, and there was no measurement of biomarker concentration in urine as an independent measure of smoking dosage. Second, the subjects were volunteers, so the results may not be generalized to the smoking population. It has been reported that smokers had smaller gray matter volumes and lower gray matter densities than nonsmokers in the prefrontal cortex bilaterally, along with smaller volumes in the left dorsal anterior cingulate cortex and lower gray matter densities in the right cerebellum.²⁹ Das et al found that lifetime use of cigarette was associated with smaller left nucleus accumbens and larger left putamen volume.³⁰ Third, because of much higher costs and longer examination time, we did not design this study to perform brain MRI to evaluate whether the brain atrophy and microvascular changes were prominent in smokers. We performed brain CT scan to evaluate the anatomic structure in this study.

CONCLUSION

There is a dose-response relationship between the number of packs smoked per day and SUR in the striatum, and between the frequency of hand tremor in the rest state and in the arm extended state. Decreased DAT binding in the striatum and increased frequency of hand tremor in smokers may have important implications for evaluating the impact of smoking on the central and peripheral nerve systems.

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