Dopamine Function in Cigarette Smokers: An [^{18}F]-DOPA PET Study

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Tobacco addiction is a global public health problem. Addiction to tobacco is thought to involve the effects of nicotine on the dopaminergic system. Only one study has previously investigated dopamine synthesis capacity in cigarette smokers. This study, exclusively in male volunteers, reported increased dopamine synthesis capacity in heavy smokers compared with non-smokers. We sought to determine whether dopamine synthesis capacity was elevated in a larger sample of cigarette smokers that included females. Dopamine synthesis capacity was measured in 15 daily moderate smokers with 15 sex- and age-matched control subjects who had never smoked tobacco. Dopamine synthesis capacity (indexed as the influx rate constant K_i^{PET}) was measured with positron emission tomography and 3,4-dihydroxy-6- ^{18}F -fluoro-*L*-phenylalanine. There was no significant group difference in dopamine synthesis capacity between smokers and non-smoker controls in the whole striatum ($t_{28}=0.64$, $p=0.53$) or any of its functional subdivisions. In smokers, there were no significant relationships between the number of cigarettes smoked per day and dopamine synthesis capacity in the whole striatum ($r=-0.23$, $p=0.41$) or any striatal subdivision. These findings indicate that moderate smoking is not associated with altered striatal dopamine synthesis capacity.

Neuropsychopharmacology (2014) 39, 2397–2404; doi:10.1038/npp.2014.87; published online 7 May 2014

INTRODUCTION

Tobacco addiction is a major global public health problem (Ezzati and Lopez, 2003). Only 3–5% of self-quitters achieve prolonged abstinence for 6–12 months after quitting (Hughes *et al*, 2004). Treatment of tobacco addiction is successful in less than 19% of cases (West *et al*, 2000), indicating that there is a pressing need to develop improved treatments (Menossi *et al*, 2013). The development of better therapies for tobacco addiction is likely to need greater understanding of the neurobiological changes associated with tobacco use. Addiction to tobacco is thought to involve the effects of nicotine, its main addictive component (Stolerman *et al*, 1995), on the dopaminergic system (Balfour *et al*, 2000; Pidoplichko *et al*, 1997) as nicotinic

receptors have been identified on nigrostriatal and mesolimbic dopaminergic neurons (Clarke and Pert, 1985). Supporting this, studies in rodents and non-human primates show that tobacco or nicotine increase dopamine neuron firing (Grenhoff *et al*, 1986; Zhang and Sulzer, 2004), increase dopamine release (Dewey *et al*, 1999; Gallezot *et al*, 2013; Marenco *et al*, 2004; Pontieri *et al*, 1996), and increase dopamine synthesis (Tsukada *et al*, 2005) in the striatum.

In humans, tobacco use has been associated with both increased striatal dopamine synthesis capacity (Salokangas *et al*, 2000) and dopamine release in response to acute cigarette use in smokers (Brody *et al*, 2004; Le Foll *et al*, 2013). However, two studies found that acute nicotine use did not elicit a significant dopamine release in smokers (Barrett *et al*, 2004; Montgomery *et al*, 2007), although these did find that the subjective hedonic response to acute nicotine was related to dopamine release. Smoking-induced dopamine release has been associated with a reduction in craving and the severity of tobacco dependence (Brody *et al*, 2004). Yet, unlike other drugs of addiction, drug-related (ie, smoking-related) cues did not result in significant dopamine release in smokers when compared with neutral images (Chiuccariello *et al*, 2013). Interestingly, one study (Busto *et al*, 2009) found that tobacco dependence was

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Received 20 December 2013; revised 13 March 2014; accepted 26 March 2014; accepted article preview online 10 April 2014

associated with reduced amphetamine-induced striatal dopamine release, although this is likely exacerbated by comorbid depression. These findings may reflect differences in the study design (Gallezot *et al*, 2013), the influence of other factors, such as sex effects, co-morbidity, or genetic variants (Dierker *et al*, 2002; Kendler *et al*, 1993; Lerman *et al*, 1998; Zhang *et al*, 2006), or the difficulty of imaging dopamine changes that are comparatively small (Egerton *et al*, 2010). In terms of other aspects of dopaminergic function, a large study on the dopamine transporter did not find an association between smoking and dopamine transporter availability (Thomsen *et al*, 2013).

As discussed above, studies indicate that striatal dopamine synthesis may be altered by nicotine exposure. Dopamine synthesis capacity can be indexed in humans using a radiolabeled dopamine precursor, L-3,4-dihydroxyphenylalanine (L-DOPA) with positron emission tomography (PET; Kumakura and Cumming, 2009). Our primary hypothesis was, therefore, that cigarette smokers would have increased dopamine synthesis capacity compared with non-smoker controls. To our knowledge, only one study has investigated dopamine synthesis capacity in cigarette smokers. This study, exclusively in male volunteers, found that striatal uptake of [^{18}F]-DOPA was 16–29% higher in smokers than non-smokers (Salokangas *et al*, 2000). However, as this sample was exclusively of males and there is evidence of sex differences in the release of dopamine in response to nicotine (Dluzen and Anderson, 1997), we sought to determine whether dopamine synthesis capacity was elevated in a larger sample of cigarette smokers that included females and did not have a history of psychiatric co-morbidity including depression and alcohol use disorders.

MATERIALS AND METHODS

A case-control design was used to compare striatal [^{18}F]-DOPA uptake in smokers to that in non-smokers. The study was conducted in accordance with the Declaration of Helsinki and followed National Research Ethics Service and the Administration of Radioactive Substances Advisory Committee approval. All participants received full information about the study and gave informed written consent to take part.

Participants

Participants were recruited through advertisements in the press. The non-smokers were matched to the smokers on the basis of age (within 5 years) and sex. Inclusion criteria for all subjects were: minimum age 18 years, good physical health with no history of major medical condition, and capacity to give written informed consent. The exclusion criteria for all participants were: presence of any significant current medical disorder or treatment including history of head injury resulting in loss of consciousness and any neurological disorder; contraindications to PET including pregnancy or breast-feeding; a diagnosis of past or current psychiatric disorders including personality disorder using the Structured Clinical Interview for DSM-IV (SCID; First *et al*, 1996) including alcohol or any other substance dependence or abuse (apart from Nicotine Use Disorders in

cigarette smokers); evidence of an At Risk Mental State for Psychosis; drug use other than alcohol or cigarettes in the 3 months before PET scanning; a family history of any psychotic disorder in first- or second-degree relatives. All participants provided urine samples to screen for drug use (Monitex HC12, Branan Medical Corporation, Irvine, California), and in women, for pregnancy test. Participants were excluded if either sample came back with positive result on the day of the scan. No subject was taking psychotropic medication at the time of study participation.

Smoking Data

Smoking data were collected via a semi-structured questionnaire for assessing exposure to cigarettes and alcohol (from the Cannabis Experiences Questionnaire interview; Barkus *et al*, 2006). The non-smoker group was defined as those with no lifetime use of tobacco.

PET

All participants were asked to not to eat or drink (except water), and refrain from alcohol for 12 h before the scan. The smokers were allowed tobacco 3 h before the scan. This time period was selected so that nicotine levels were at steady state (Benowitz *et al*, 1982). In addition, this is a similar time period to the only other study that has investigated dopamine synthesis capacity in smokers (Salokangas *et al*, 2000). Less than 2 h would coincide with peak plasma nicotine levels and longer durations would likely be measuring the dopamine system in a state of nicotine withdrawal. Imaging data from the PET scans were obtained on a Siemens CTI ECAT HR + 962 PET scanner (Siemens, Erlanger, Germany) in three-dimensional mode with an axial field of view of 15.5 cm. One hour before the scan, participants received 400 mg entacapone, a peripheral catechol-O-methyltransferase inhibitor, and 150 mg carbidopa, a peripheral aromatic acid decarboxylase inhibitor, in order to increase specific signal detection, as these compounds decrease the formation of radiolabeled metabolites that may cross the blood-brain barrier (Cumming *et al*, 1993; Guttman *et al*, 1993). A 10 min transmission scan was conducted before the radiotracer injection using a 150-MBq cesium-137 rotating point source to correct for scatter and attenuation. Participants were positioned in the scanner with the orbitomeatal line parallel to the transaxial plane of the tomograph. Head position was marked and monitored via laser crosshairs and a camera, and movement was minimized using a head strap.

A 17 MeV GE PET-trace cyclotron was used for radionuclide production. The gas target was filled with $^{18}\text{O}_2$ and bombarded at 40 μA for 30 min followed by a passivation bombardment of 0.1% F_2 in argon at 20 μA for 20 min. This produced [^{18}F]-F by the $^{18}\text{O}(\text{p},\text{n})$ ^{18}F reaction. An electrophilic fluorination procedure was then used to synthesize 6-[^{18}F]fluoro-L-DOPA. In brief, [^{18}F] F_2 was bubbled through a solution of 6-trimethylstannyl-L-DOPA (60 mg) stirring in Deutero-chloroform (5 ml) over 20 min at 5 $^\circ\text{C}$. 6 M HCl (2 ml) was added and the chloroform evaporated at 70 $^\circ\text{C}$. The resulting aqueous mixture was heated at reflux for 10 min before allowing to cool. The cooled crude mixture was purified by semi-prep high-pressure liquid chromatography.

graphy polymer X column eluting with ammonium acetate buffer. The peak corresponding to [^{18}F]-L-DOPA eluted at 15 min was stabilized with 1 mg ascorbic acid and sodium phosphate dibasic. Typical yields were 2.96–3.33 GBq. For quality assurance purposes, a sample was taken from each synthesis and analyzed by reverse phase high-pressure liquid chromatography to confirm identity and purity. To be able to proceed with the injection, a radiochemical purity of 95.0% or higher was required. Approximately 180 MBq of [^{18}F]-DOPA was administered as a bolus intravenous injection 30 s after the start of the emission scan. Emission data were acquired as 26 frames of increasing duration over the 90 min scan. This comprised a 30-s background frame, 4 60-s frames, 3 120-s frames, 3 180-s frames, and finally 15 300-s frames.

Image Analysis

To correct for head movement in the scanner, non-attenuation-corrected dynamic images were denoised using a level 2, order 64 Battle-Lemarie wavelet filter. We used nonattenuation-corrected images used for the realignment algorithm as they include greater scalp signal, improving re-alignment compared with attenuated-corrected images (Turkheimer *et al*, 1999). Frames were realigned to a single 'reference' frame, acquired 10 min post-injection, employing a mutual information algorithm (Studholme *et al*, 1996). The transformation parameters were then applied to the corresponding attenuated-corrected dynamic images. The realigned frames were then summated, creating a movement-corrected dynamic image, which was used in the analysis. The cerebellar reference region (Kumakura and Cumming, 2009) was defined using a probabilistic atlas (Martinez *et al*, 2003), and as previously described, regions of interest (ROI) in the whole striatum and its functional sub-divisions were delineated to create an ROI map (Egerton *et al*, 2010). The functional subdivisions of the striatum reflect the topographical arrangement of corticostriatal projections. Projections to the sensorimotor striatum come from the motor cortex and related areas for instance the premotor cortex, primary motor cortex, and supplementary motor cortex; projections to the associative striatum start in associative regions such as dorsolateral prefrontal cortex; and projections to the limbic striatum are from limbic areas such as the amygdala and hippocampus (Haber, 2003). SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>) was then used to normalize the ROI map together with the tracer-specific ([^{18}F]-DOPA) template (Egerton *et al*, 2010, Howes *et al*, 2009) to each individual PET summation image. This nonlinear transformation procedure allowed ROIs to be automatically placed on individual [^{18}F]-DOPA PET dynamic images. The influx constant (K_i^{cer} , written as K_i in some previous publications (Howes *et al*, 2009)) for the entire striatal ROI and the functional subdivisions bilaterally were calculated compared with uptake in the reference region using a graphical approach adapted for a reference tissue input function (Egerton *et al*, 2010).

Statistical Analysis

Normality of distribution and homogeneity of variance were assessed using Kolmogorov–Smirnov and Levene's tests,

respectively. Group (smoker *vs* non-smoker) differences in demographic and imaging variables were determined using independent samples *t*-tests for normally distributed data, Mann–Witney *U*-tests for non-normally distributed data, and the χ^2 test for dichotomous variables. The influence of sex on group differences in K_i^{cer} was determined using a two-way analysis of variance. Within the smoker group, the relationship between K_i^{cer} and level of cigarette consumption was tested using Pearson's product-moment correlation coefficient. A two-tailed significance level of $p = 0.05$ was employed throughout. A power calculation determined that we needed a sample size of 15 per group to have 80% or greater power to detect the effect size reported in the Salokangas *et al*, study (Cohen's $d = 1.1$) at this significance level.

RESULTS

Subject Characteristics and Scan Parameters

Fifteen smokers were recruited into the study. All smokers consumed tobacco as a cigarette. Mean (SD) cigarette consumption was 8.1 (4.1) per day (range: 1–17). Twelve smokers met DSM-IV(TR) criteria for Nicotine Dependence. Mean (SD) cigarette consumption was 9.6 (2.9) per day in smokers who met Dependency criteria (range: 5–17). Mean (SD) cigarette consumption was 2.0 (1.0) per day in smokers who did not meet criteria.

Fifteen non-smoker control subjects were matched to the smoker group for age (± 5 years) and sex. Group demographics are reported in Table 1. Urine drug screens were negative for all substances (cannabis, amphetamine, opiates, cocaine, methamphetamine, benzodiazepines) in every subject.

Subjects were well matched for age and sex. There was no significant group difference in the amount of radioactivity or specific activity of [^{18}F]-DOPA administered (Table 1). No subjects had a history of alcohol dependence or abuse according to DSM-IV(TR) criteria and subjects were well matched for alcohol use. There was no relationship between age and K_i^{cer} in the whole striatum ($r = -0.10$, $p = 0.62$) or its subdivisions in the whole sample or in either group (data available on request).

Striatal Dopaminergic Function

There was no significant group difference in K_i^{cer} in the whole striatum (Figure 1), or any striatal subdivision (Table 2). No significant differences in K_i^{cer} were detected after removing the three smokers who did not meet DSM-IV(TR) diagnostic criteria for nicotine dependency from the analysis ($t_{25} = 0.85$, $p = 0.40$).

The Relationship between Striatal Dopamine Synthesis Capacity and Tobacco Use

In smokers, there were no significant relationships between the number of cigarettes smoked per day and K_i^{cer} in the whole striatum ($r = -0.23$, $p = 0.41$; Figure 2), or any striatal subdivision (associative: $r = -0.16$, $p = 0.57$; sensorimotor: $r = -0.33$, $p = 0.23$; limbic: $r = -0.22$, $p = 0.44$).

To examine whether nicotine dependency was specifically associated with elevated K_i^{cer} , we divided the tobacco user

Table 1 Sample Characteristics and Scan Parameters

	Non-smoker controls	Smokers	<i>p</i> ^a
<i>Sample characteristic</i>			
Age (years), mean (SD)	29.5 (11.1)	29.9 (10.3)	0.92
Sex (m:f) (<i>n</i>)	10:5	10:5	1.00
Ethnicity ^b (<i>n</i>)	8WB, 3BB, 2AB, 1ME, 1OE	12WB, 1BB, 1AB, 1ME	0.12
Tobacco smokers (<i>n</i>)	0	15	0.00
Tobacco use (cigarettes/day), mean(SD)	0.0 (0.0)	8.1 (4.1)	0.00
Cigarettes smoked before PET scan, mean (SD)	0.0 (0.0)	0.8 (0.4)	0.00
Alcohol users (<i>n</i>)	13	11	0.36
Alcohol ^c use (UK alcohol units/week), mean (SD)	7.1 (8.7)	11.2 (8.7)	0.21
<i>Scan parameter</i>			
Injected dose (MBq), mean (SD)	182.4	182.7	0.87
Specific activity (MBq/μmol), mean (SD)	30.1	27.5	0.62

Abbreviations: AB, Asian British; BB, black British; ME, mixed ethnicity; OE, other ethnicity; WB, white British.

^aIndependent-samples *t*-tests for variables with normal data distributions; Mann-Whitney *U*-tests for variables with non-normal data distributions; χ^2 tests for dichotomous variables.

^bGroups were compared on a dichotomized ethnicity variable (white British vs ethnic minority).

^c1 UK alcohol unit = 10 ml (~7.88 g) alcohol.

Figure 1 Whole striatal dopamine synthesis capacity (indexed as the influx rate constant K_i^{cer}) in smokers compared to non-smokers. Error bars indicate standard deviations.

Figure 2 The relationship between tobacco use and dopamine synthesis capacity (indexed as the influx rate constant K_i^{cer}) in smokers.

Table 2 [18F]-DOPA K_i^{cer} (min^{-1}) by Group

ROI	Non-smoker controls (<i>n</i> = 15)		Smokers (<i>n</i> = 15)		Group comparison ^a	
	Mean	SD	Mean	SD	<i>t</i> _{df}	<i>p</i>
STR	0.0130	0.0010	0.0128	0.0012	0.64 ₂₈	0.53
AST	0.0126	0.0010	0.0122	0.0011	0.84 ₂₈	0.41
LST	0.0132	0.0017	0.0135	0.0012	0.63 ₂₈	0.53
SMST	0.0141	0.0011	0.0138	0.0016	0.67 ₂₈	0.51

Abbreviations: AST, associative striatum; K_i^{cer} , influx rate constant; LST, limbic striatum; ROI, region of interest; SMST, sensorimotor striatum; STR, whole striatum.

^aIndependent-samples *t*-tests.

group into subjects who met DSM-IV(TR) diagnostic criteria for nicotine dependency (*n* = 12), and those who did not meet criteria (*n* = 3). Mean (SD) K_i^{cer} was 0.0127

(0.0010) min^{-1} in smokers meeting Nicotine Dependence criteria and 0.0131 (0.0019) min^{-1} in smokers who did not meet criteria. *t*-Tests showed no significant differences between the nicotine dependency sub-group and non-smoker controls ($t_{25} = 0.85$, $p = 0.40$). There was no significant relationship between tobacco use and dopamine synthesis capacity in the whole striatum ($r = 0.18$, $p = 0.57$) or any of its functional subdivisions (data available on request) within the nicotine-dependent sub-group.

Sex

We performed a further explorative analysis to examine for possible sex effects. Mean (SD) K_i^{cer} was 0.0127 (0.0008) min^{-1} in females and 0.0130 (0.0012) min^{-1} in males. Among males, mean (SD) K_i^{cer} was 0.0130 (0.0013) min^{-1} in smokers and 0.0131 (0.0010) min^{-1} in non-smokers. Among females, mean (SD) K_i^{cer} was 0.0125 (0.0010) min^{-1}

in smokers and 0.0130 (0.0006) min^{-1} in non-smokers. Two-way analysis of variance did not reveal a significant interaction between smoking status and sex on dopamine synthesis capacity in the whole striatum ($F_{1,26} = 0.23$, $p = 0.64$) or any functional subdivision (associative striatum: $F_{1,26} = 0.08$, $p = 0.79$; sensorimotor striatum: $F_{1,26} = 0.34$, $p = 0.54$; limbic striatum: $F_{1,26} = 0.73$, $p = 0.40$).

DISCUSSION

This study found no evidence for altered striatal dopamine synthesis in tobacco smokers compared with non-smokers, or relationship between the levels of daily cigarette smoking and dopamine synthesis capacity. Furthermore, we did not find an effect of nicotine dependence on dopamine synthesis capacity. Our findings are therefore not consistent with our hypothesis that dopamine synthesis capacity would be elevated in smokers compared with non-smokers.

These negative findings are in contrast to a previous report of elevated dopamine synthesis capacity in 9 male smokers compared with 10 non-smokers (Salokangas *et al*, 2000). Although striatal dopamine synthesis capacity may be higher in females (Laakso *et al*, 2002), this was not evident in our sample. The subjects in the study by Salokangas *et al* were heavy smokers (at least 15 cigarettes/day, mean 19.8 cigarettes/day compared with mean 8.1 cigarettes/day in our study), which could explain the difference with our findings. Although we found no evidence of a relationship between K_i^{cer} and the level of daily cigarette consumption, this may indicate that elevations in presynaptic dopamine synthesis capacity are only apparent in heavy smokers.

The study by Salokangas *et al* (2000) used the same methodology as a previous study by Hietala *et al* (1999), ie, Carbidopa 100 mg only was administered 90 min before PET scan (Personal Communication from Professor Salokangas), followed by measurement of radiolabeled metabolites in the arterial input function. This is in comparison to the carbidopa 150 mg and entacapone 400 mg administered 1 h before PET scan followed by a cerebellar reference region approach in the present study. To our knowledge, data on the effects of smoking on the pharmacodynamics of entacapone are lacking. Entacapone undergoes rapid hepatic metabolism via the uridine 5'-diphospho-glucuronosyl-transferase pathway (Lautala *et al*, 2000). Data from studies in humans (Bock and Köhle, 2004) and mice models (Villard *et al*, 1998) indicate that cigarette smoke is a potent inducer of uridine 5'-diphospho-glucuronosyltransferase, which would thus lead to a faster elimination of entacapone and therefore a potential reduction in plasma [^{18}F]-DOPA in smokers *vs* controls whom have had entacapone administered. As our reference region approach theoretically eliminates the plasma input function, we would predict the main effect of any potential reduction in plasma [^{18}F]-DOPA to result in increased variability of K_i^{cer} without altering mean K_i^{cer} . However, there are limited data directly comparing K_i values obtained via a tissue reference region and arterial plasma input function method, as was the case in the study by Salokangas *et al* (2000). Sossi *et al* (2003) reported a comparison between a reference region and arterial input function approach. In that study, Sossi *et al* used the occipital lobe as the reference region, rather than

the cerebellum used in our study. Therefore, it remains possible that a difference in entacapone metabolism in smokers may be underlying the disparity in results between our study and that of Salokangas *et al* (2000). Nevertheless, the entry into and exit from the brain of radiolabeled plasma metabolites may affect graphical analysis (Boyes *et al*, 1986; Cumming *et al*, 1987) and could bias results if metabolism is selectively altered in one group. Compared with non-smokers, smokers have reduced CSF levels of the dopamine metabolite homovanillic acid (Geraciotti *et al*, 1999) and there is evidence of reduced MAO-A and MAO-B activity in smokers (Fowler *et al*, 1996a, b). However, as these differences would, if anything, reduces the production of radiolabeled metabolites in smokers, they are unlikely to explain the failure to detect an elevation in smokers. In summary, even if entacapone clearance is higher in our smoker group, we remain unable to conclude that it would be sufficient to impact metabolite production within our experimental window. Furthermore, even if there was a sufficient impact on metabolite production, our use of a reference region approach would be expected to be sufficiently robust to overcome this problem.

Survey data in Great Britain indicate that over the last few decades there has been a gradual decline in the number of cigarettes consumed per day among smokers, such that the average number of cigarettes smoked per day is now 12 for men and 11 for women (Office for National Statistics, 2013). Our sample of moderate smokers is therefore in the same range as that of the general population. Overall our findings and those of Salokangas *et al* thus indicate that there is no markedly altered dopamine function in moderate smokers, but alterations are apparent in heavy smokers. A further contributing factor for the discrepancy in findings from those of the study by Salokangas *et al* and the present study is that the nicotine content of cigarettes has decreased since the former. However, we did not collect data on the type of cigarette consumed by each tobacco-smoking subject, which would have enabled an estimation of the amount of nicotine consumed. Despite proposals for nicotine reduction policies (Benowitz and Henningfield, 1994), which have intended for the nicotine content of cigarettes to be reduced, there is some evidence that the nicotine yield of cigarettes in American brands may, in fact, have increased since the Salokangas study (Connolly *et al*, 2007). Future studies assessing both the effects of heavy *vs* moderate smoking and nicotine dose of cigarettes on dopaminergic function are therefore warranted.

Study Limitations

Although our sample size was larger than the only other study to investigate dopamine synthesis capacity in smokers, it is important to consider the possibility of a type II error in our findings. We had 84% power to detect the effect size (Cohen's $d = 1.12$) seen in the Salokangas *et al* study, which is above the 80% power threshold conventionally considered adequate. Nevertheless, even at this power, there is a 16% chance that a true effect of this magnitude has been missed. As we only included moderate smokers, a limitation of our study would be that we did not include a group of heavy smokers for comparison. A potential limitation of the correlation between cigarette use and

dopamine synthesis capacity is that seven of the smokers in our study consumed 10 cigarettes per day, which likely reflects the fact that tobacco in the United Kingdom is sold in packets of 10 and 20 cigarettes, but limits the power of the correlational analysis. Our sample contained five female subjects per group and so was underpowered to detect sex-group interactions, indicating that these analyses should only be considered exploratory. Gonadal hormones may influence dopaminergic function. However, we did not assess this or phase of the menstrual cycle in the females.

A further limitation of our study is that we did not include the Fagerström Test for Nicotine Dependence, which would have enabled the exploration of the relationships between dopamine synthesis capacity and subjective craving. Likewise, we did not measure plasma nicotine, cotinine, or carbon dioxide levels. Future studies would therefore benefit from including these measures in larger sample sizes.

Implications for Understanding Tobacco Addiction

The role of the dopamine system in drug reinforcement has long been accepted from animal studies (eg, Koob, 1992) and there is mounting evidence that dysregulated dopamine function is central to addiction behaviors in humans (as reviewed by Volkow *et al*, 2011). There is growing evidence that chronic drug abuse is associated with abnormal striatal dopaminergic functioning in humans, as has been found with alcohol (Heinz *et al*, 2005), cannabis (Bloomfield *et al*, 2013), cocaine (Wu *et al*, 1997), methamphetamine (Wang *et al*, 2012), and ecstasy (Tai *et al*, 2011). However, our study suggests that dopamine dysregulation may only become apparent at higher levels of use, either because it is below the level of detection with more moderate use, or because it is a cumulative consequence of heavy use.

CONCLUSIONS

This study found that moderate smoking was not associated with marked effects on striatal dopamine synthesis capacity, in contrast to a previous finding of elevated dopamine synthesis capacity in heavy smokers. Further studies in smokers of presynaptic dopaminergic function using heavy and moderate smokers are warranted to determine whether dopaminergic effects only become evident with heavier use.

FUNDING AND DISCLOSURE

Dr Bloomfield and Dr Mouchlianitis receive funding from the Medical Research Council (UK). Dr Howes has received research funding from the Medical Research Council (UK) (Grant: MC-A656-5QD30) and a National Institute of Health Research Biomedical Research Council grant to King's College London for this study. He has received investigator-led charitable research funding or has been on the speaker bureaux for Astra-Zeneca, BMS, Eli Lilly, and Janssen Cilag. The remaining authors declared no conflict of interest.

ACKNOWLEDGEMENTS

We thank our subjects and the staff of GE Imanet for their assistance with the positron emission tomography scans, in

particular Ms Hope McDevitt, Mr Andrew Blyth, Ms Andreanna Williams, and Ms Stephanie McKnight.

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