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ARTICLE

Gender: a major determinant of brain response to nicotine

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Abstract

Biological factors responsible for nicotine initiation and dependence are largely unknown. Men and women smoke differently, and may smoke for different reasons. Brain metabolic response to nicotine may explain gender differences in nicotine use. We used FDG-PET to measure brain metabolic response on placebo and following nicotine administered by patch in 42 females and 77 males (smokers and non-smokers) while performing a Continuous Performance Task (CPT) or the Bushman Competition and Retaliation Task (CRT). Nicotine administration affected brain metabolism much differently in males and females, and these differences were dependent on task and smoking history. In the placebo condition female smokers performing the CPT and female non-smokers performing the CRT consistently had higher brain metabolism than males, especially in the entire prefrontal system and the mid and anterior temporal lobe, language cortices, and related subcortical systems. The overall effect of nicotine was to decrease these gender differences in brain metabolism.

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Introduction

Accumulating evidence shows that males and females may smoke at different rates and for different reasons. In general, females take fewer and shorter cigarette puffs, are less sensitive to some of nicotine's effects, are less successful with nicotine replacement therapy, and are more sensitive to smoking cues (CDC, 2003; Delfino et al., 2001; NIDA, 2000). We have been interested in the possibility of a gender difference in brain metabolic response to nicotine as a factor in understanding these gender differences. Since we have found a difference in metabolism in response to nicotine between smokers and non-smokers (Fallon et al., 2004), we also considered gender effects in smokers and non-smokers, both collectively and separately. The imaging tasks included a hostility/retaliatory task and an attentional/impulsivity task given the strong association of these personality characteristics with nicotine susceptibility (Barefoot et al., 1991; Fallon et al., 2004; Gilbert and Gilbert, 1995; Golding and Mangan, 1982; Jamner et al., 1999; Jenks, 1992; Lipkus et al., 1994; Netter et al., 1998; Scherwitz et al., 1992; Whiteman et al., 1997; Williams, 1973; Zuckerman et al., 1990). Our hypotheses integrate these findings, proposing an interaction between gender, task, and nicotine.

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Methods

Using fluoro-deoxyglucose–position emission tomography (FDG-PET), we contrasted regional brain metabolic response to nicotine patch in smokers and non-smokers while the subjects performed a Continuous Performance Task (CPT) or the Bushman Competition and Retaliatory Task (CRT). Subjects were recruited by advertisement and screened for absence of personal or family major psychiatric illness and absence of medically significant, acute or chronic, illness requiring medication. Smoking history was obtained and subjects having smoked fewer than 10 cigarettes in their life and none in the previous 2 years were classified as non-smokers. Smokers smoked at least 10 cigarettes on a daily basis for at least 1 year and less than two packs per day. In total, 119 subjects

participated (77 males and 42 females). Sixty-four non-smokers completed all PET study procedures with both a placebo and 3.5-mg nicotine patch, and 55 smokers completed the procedures with a placebo, 3.5-mg nicotine patch, and 21-mg nicotine patch. (The 21-mg patch is approximately equivalent to half the plasma level obtained from smoking a standard cigarette.)

We chose a patch delivery of nicotine in non-smokers in order to remove the cueing and non-nicotine-related effects of smoking. Subjects' levels of brain metabolism with nicotine and placebo were compared in a double-blind, random assignment design. Nicotine (SmithKline Beecham, NicoDerm CQ) was administered at 3.5 or 21 mg, 3.5 h before injection of 5 mCi of FDG. Preliminary pilot testing in non-smokers demonstrated that some subjects, especially females, developed nausea and vomiting on 7 mg, and most subjects could discern which substance was given (nicotine vs. placebo). The low dose of 3.5 mg minimized both of these potential problems. During the FDG uptake, subjects performed a computer task that required sustained visual attention, response inhibition, and reaction time (CPT) or the Bushman CRT, which involved retaliatory responding by the subjects but not impulsivity-related behaviour (Baker et al., 1995; Bushman, 1995; Fallon et al., 2004). In the CPT, the subject views a series of blurred numbers presented a few seconds apart. Target numbers appear at intervals and the subject must remain vigilant to detect these targets with a button press (Nuechterlein et al., 1983). The Bushman task is used to provoke aggressive, retaliatory responding by participants. The subject competes with an 'opponent' in a reaction-time task in which the loser receives a blast of unpleasant noise. The object is to determine who can react more quickly to a red signal presented on a computer monitor. The person who presses his/her computer mouse key more slowly receives a burst of white noise while the subject depresses the mouse button delivered through headphones. The subject sets the level of static noise that he/she wants his/her 'opponent' to receive if the opponent's response is slower (a zero intensity level is included to provide a non-aggressive response alternative, and 10 is the most aggressive response. After the trial, the program displays the noise level that the subject's 'opponent' had set for him or her to receive for that trial. For the following trial, the subject can set the loudness and/or the duration of the sound blast to be delivered to the opponent.

Thirty PET slices at 6.5-mm intervals were obtained to cover the entire brain. Differences in regional FDG uptake were analysed by using statistical parametric mapping software (SPM 99; Wellcome Department of Cognitive Neurology, University College, London, UK), with voxel values at a threshold of $p < 0.025$ to correct for multiple comparisons, as described in detail by Fallon et al. (2004). The design matrix included as covariates global metabolic activity, age, handedness, plasma nicotine and cotinine concentrations (Jacob et al., 1981, 2000) to control statistically for the potential effects of these variables. Images were spatially normalized to the SPM standard brain template corresponding to the space defined by the Montreal Neurological Institute (MNI) brain atlas. Coordinates of significant activations were converted from MNI space to the space defined by Talairach and Tournoux to facilitate more widely used anatomical localization nomenclature using a nonlinear combination of two linear transformations (MRC, 2004). Coordinates above the anterior commissure were transformed using the following three linear equations: $X' = 0.9900X$, $Y' = 0.9688Y + 0.0460Z$, $Z' = -0.0485Y + 0.9189Z$. Coordinates below the anterior commissure where transformed by: $X' = 0.9900X$, $Y' = 0.9688Y + 0.0420Z$, $Z' = -0.0485Y + 0.8390Z$, different transformations were used above and below the AC/PC line because a single transform does not adequately account for the nonlinearity of the match between the Talairach and MNI brain in the dorsal vs. ventral aspects of the brain.

After the initial comparison of males and females on placebo, we separated smokers from non-smokers because of their differential experience with nicotine and our previous studies contrasting smokers and non-smokers (Fallon et al., 2004). Separate analyses were done for smokers and non-smokers for the CRT and CPT.

Results

Biochemical and behavioural results

There were no gender differences in plasma nicotine and cotinine levels or pre-scan CO measurements or Fagerstrom measures of nicotine dependence (p's > 0.36). During the CPT there were no significant differences between males and females on any performance measure (see Table 1). During the CRT males increased *intensity* of retaliation more than females ($p < 0.05$), and females increased *duration* of retaliation more than males. In post-hoc subgroup analyses the difference between males and females was significant for non-smokers ($p < 0.02$) but not for smokers ($p < 0.30$). Controlling for performance measures did not change the overall PET imaging results.

Table 1. Comparisons between males and females on performance on the CPT (attentional/impulsivity task) and CRT (Bushman hostility/retaliatory task) during FDG uptake

Task	Measure	Gender	Placebo mean	S.D.	Main effect
CPT	*D'*	M	1.54	0.77	ns
		F	1.70	0.62	
	Correct (240 targets)	M	148.28	52.56	ns
		F	155.50	59.98	
	Incorrect (240 targets)	M	91.72	52.56	ns
		F	84.50	59.98	
	False alarms (980 targets)	M	97.97	76.74	ns
		F	84.73	47.71	
	Response bias	M	0.41	0.55	ns
		F	0.45	0.67	
CRT	Intensity (1–10)	M	6.31	2.07	$F(1, 134) = 6.1$,
		F	5.06	1.00	$p < 0.02$
	Duration (ms)	M	197.46	84.39	$F(1, 134) = 7.4$,
		F	293.43	172.95	$p < 0.01$
	Reaction time (ms)	M	275.53	87.94	ns
		F	289.25	124.44	

PET imaging results

Nicotine affected males and females much differently (see Figures 1–3 and Table 2). All of the metabolic differences between males and females reported herein involved higher glucose metabolic rates in females. Most of these differences were bilateral. Regardless of task, in the placebo conditions (Figure 1a, c) females consistently had higher brain metabolism, especially in the entire prefrontal system and the mid and anterior temporal lobe, language cortices, and related subcortical systems. Although nicotine administration affected metabolism in males and females differently, the overall effect of nicotine was to eliminate the differences between males and females in the CPT (Figure 1b), but to a lesser degree in the CRT, when non-smokers and smokers are combined (Figure 1d).

CPT

In *non-smokers on the CPT* there were few differences in brain metabolism between males and females receiving the placebo patch (Figure 2a).

In *smokers on the CPT*, the differences in brain metabolism between males and females receiving the placebo patch were greatly exaggerated and included sectors of virtually all areas of the brain (Figure 2b and Table 2a). The metabolic increases in females were concentrated in the cortical and subcortical prefrontal system, i.e. orbital cortex, dorsal prefrontal cortex (the superior and middle frontal gyri), DLPFC (the central two-thirds of the middle frontal gyrus, corresponding to Brodmann area 46), posterior medial thalamus, ventral caudate, nucleus accumbens, anterior cingulate occipital cortex (the latter four out of plane on the figure), and the receptive and premotor language areas. The differences in brain metabolism between male and female smokers were essentially eliminated by both the 3.5- and 21-mg nicotine patches in smokers (Figure 2d).

In summary, most of the differences in metabolism between males and females while performing the CPT were found in the smokers on placebo. With nicotine, these differences largely disappeared.

CRT

A different pattern is observed with the CRT (Figure 3). In *non-smokers on the CRT*, brain metabolism in sectors of virtually all areas of the brain was higher in females while performing the CRT and receiving the placebo patch (Figure 3a and Table 2b). These gender differences in brain metabolism in non-smokers were virtually eliminated by the 3.5-mg nicotine patch (Figure 3c). In *smokers on the CRT*, there were very few differences between males and females when receiving placebo (Figure 3b); with nicotine, there were virtually no metabolic differences (Figure 3d). Post-hoc analyses confirmed that the

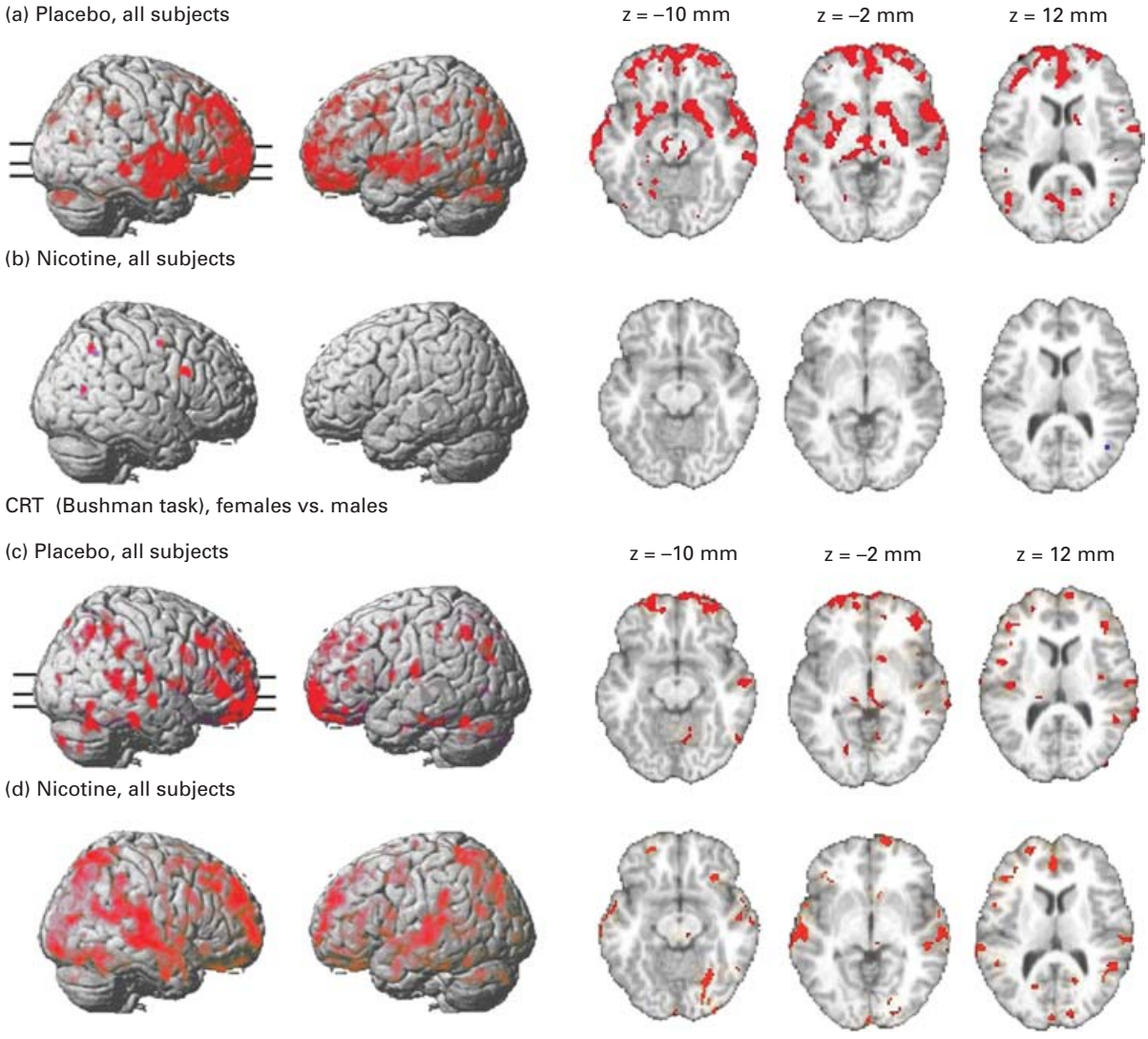

Figure 1. Rows (a)–(d) represent metabolic differences between males and females while performing the CPT (attentional task) [rows (a) and (b)] or the CRT (Bushman Competition and Retaliation Task) [rows (c) and (d)]. The first two columns represent the lateral cortical surfaces with three representative axial sections shown in the three figures on the right (z level -10, -2, $+12$ mm, relative to the cantho-meatal plane, respectively indicated by the tic marks on the surface rendering). The left and right sides of the images correspond to the left and right sides of the brain. Red indicates the pixels that have significantly ($p < 0.025$) increased metabolic rate in females relative to males on placebo [rows (a) and (c)] and on nicotine [rows (b) and (d)].

gender differences in response to nicotine is not a consequence of an effect or lack of effect in either gender but rather an interaction between gender, nicotine, and task.

Discussion

Yoshii et al. (1988), but not Kawachi et al. (2002), observed higher brain metabolism in females at rest (i.e. no task). Gender differences in brain function have been reported for memory, emotional memory, facial recognition, and visuospatial tasks (Cahill et al., 2001; Weiss et al., 2003), although no such differences have been reported for either the CPT or CRT. The gender differences in effects of nicotine on brain metabolism are largely unstudied, despite reported gender differences in nicotine use. Staley et al. (2001) found higher dopamine and serotonin transporter availability in

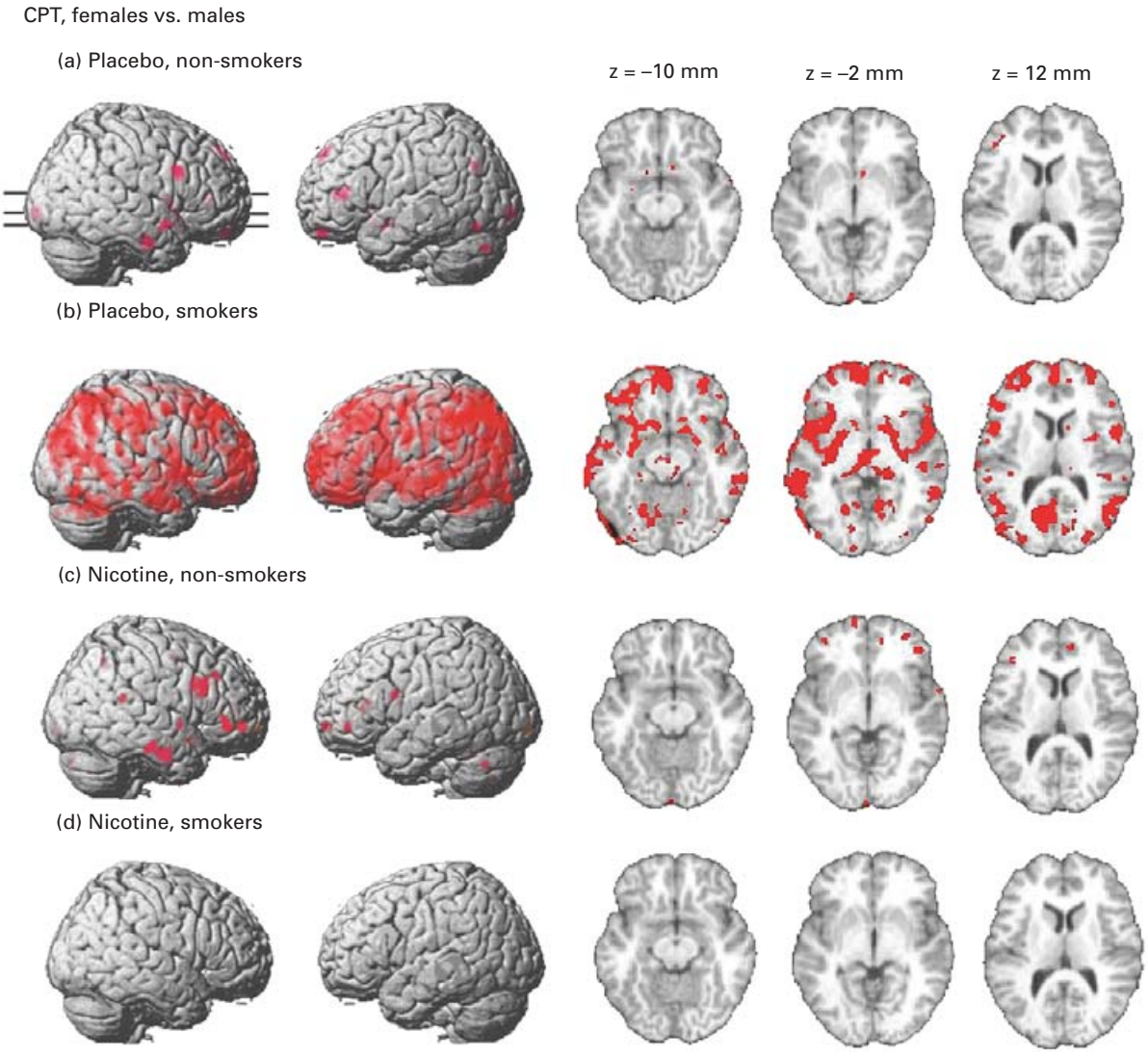

Figure 2. Rows (a)–(d) represent the metabolic differences between males and females while performing the CPT (attentional/impulsivity task). The columns represent the lateral cortical surfaces with three representative axial sections (z level −10, −2, +12 mm, relative to the cantho-meatal plane respectively), indicated by the tic marks. The left and right sides of the images correspond to the left and right sides of the brain. Red indicates the pixels that have significantly ($p < 0.025$) increased metabolic rate in females relative to males on placebo [row (a), non-smokers; row (b), smokers], on nicotine [row (c), non-smokers; row (d), smokers].

females and File et al. (2001) found that nicotine decreased negative mood ratings in females and increased them in males. Polymorphisms in the serotonin transporter gene have been linked to depression only in the presence of chronic stress, demonstrating an interaction between the serotonin transporter, mood, and environment (Caspi et al., 2003). Gender differences have also been reported for depression and hostility. Personality traits are also linked with nicotine dependence/susceptibility (Fallon et al., 2004).

We report higher brain metabolism in females during both the CPT and CRT. Nicotine eliminated the higher brain metabolism seen in females compared to males on placebo during the CPT (Figure 1b), but not the CRT (Figure 1d). Combining smokers and non-smokers, however, is inappropriate because we have shown that smoking history changes brain metabolic response to nicotine (Fallon et al., 2004). Therefore, once we considered the effects of gender separately in smokers and non-smokers, any gender differences

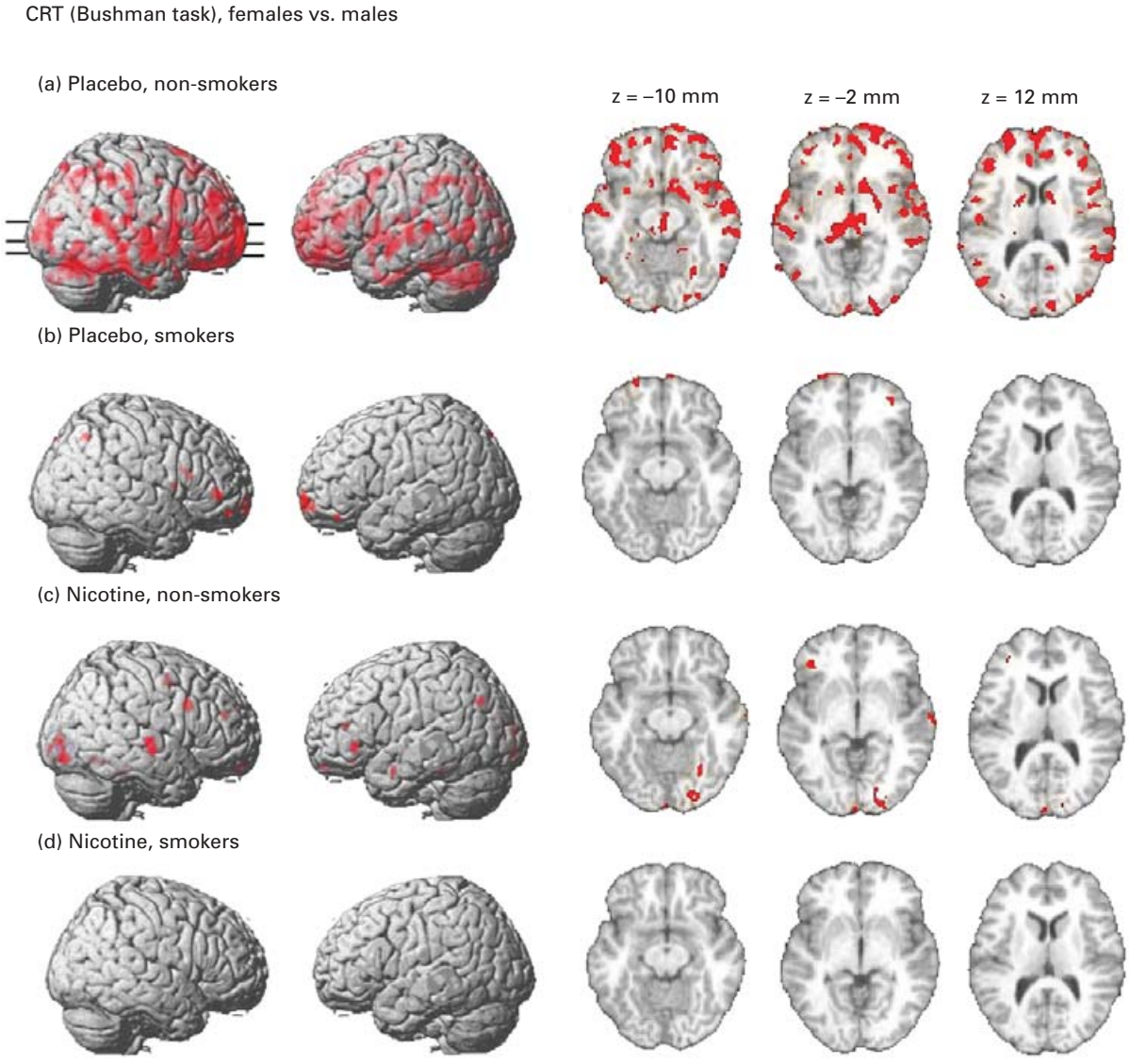

Figure 3. Rows (a)–(d) represent the metabolic differences between males and females while performing the Bushman CRT (hostility/retaliatory task). The columns represent the lateral cortical surfaces with three representative axial sections (z level −10, −2, +12 mm, relative to the cantho-meatal plane respectively), indicated by the tic marks. The left and right sides of the images correspond to the left and right sides of the brain. Red indicates the pixels that have significantly ($p < 0.025$) increased metabolic rate in females relative to males on placebo [row (a), non-smokers; row (b), smokers], on nicotine [row (c), non-smokers; row (d), smokers].

in either smokers or non-smokers that were observed on placebo, with the CPT or CRT, were eliminated or greatly reduced with nicotine. Specifically, with the CPT, higher metabolism was seen in female smokers relative to male smokers, which was eliminated by nicotine. With the CRT, higher metabolism was seen in female non-smokers relative to male non-smokers, which was eliminated by nicotine. The higher metabolism observed with placebo occurred primarily in the prefrontal, temporal, and inferior parietal lobe systems, including those areas involving choice, attention, short-term memory, executive function, mood, and language. These differences were reversed by nicotine.

The results of the present study demonstrate the importance of considering gender in understanding the behavioural, physiological, and brain metabolic effects that are associated with nicotine susceptibility/dependence in addition to smoking history, and

Table 2. Comparisons between male and female smokers on placebo during a CPT (a), and male and female non-smokers on placebo during a CRT (b)

Tailarach functional area specification	Hemisphere	x	y	z	Z score	*t* score
(a) CPT						
Temporal lobe, middle temporal gyrus	Left	−50	−48	6	3.025	3.458
Parietal lobe, precuneus	Left	−14	−66	40	2.999	3.42
Limbic lobe, sub-gyral	Right	16	−31	−3	2.808	3.154
Sub-lobar, thalamus, pulvinar	Right	18	−31	7	2.659	2.954
Superior temporal, gyrus, BA 22	Right	53	6	0	2.664	2.961
Frontal lobe, precentral gyrus	Right	53	4	11	2.491	2.734
Occipital lobe, inferior occipital gyrus, BA 18	Left	−26	−86	−13	2.587	2.858
Occipital lobe, lingual gyrus	Left	−26	−80	−6	2.236	2.413
Anterior lobe, culmen	Right	20	−49	−14	2.517	2.768
Posterior lobe, uvula	Right	16	−87	−24	2.457	2.691
Limbic lobe, anterior cingulate, BA 10	Right	14	50	−1	2.427	2.652
Frontal lobe, precentral gyrus, BA 6	Right	50	2	46	2.333	2.534
Frontal lobe, precentral gyrus	Right	32	−10	63	2.318	2.516
Temporal lobe, fusiform gyrus	Right	51	−7	−25	2.308	2.503
Frontal lobe, sub-gyral	Right	46	22	17	2.293	2.484
Frontal lobe, inferior frontal gyrus	Right	50	30	10	2.09	2.235
Frontal lobe, middle frontal gyrus	Right	28	16	40	2.266	2.45
Frontal lobe, middle frontal gyrus	Right	32	4	46	2.195	2.363
Temporal lobe, superior temporal gyrus, BA 22	Right	67	−9	6	2.193	2.361
Frontal lobe, superior frontal gyrus, BA 6	Left	−26	−3	63	2.18	2.345
Frontal lobe, inferior frontal gyrus, BA 47	Right	38	22	−16	2.153	2.312
Frontal lobe, inferior frontal gyrus, BA 47	Right	32	19	−8	2.114	2.264
Insula, BA 13	Right	32	21	1	2.072	2.213
Temporal lobe, superior temporal gyrus	Right	57	−36	17	2.151	2.31
Frontal lobe, middle frontal gyrus	Right	48	38	−9	2.111	2.26
Cuneus, BA 17	Left	−10	−95	5	2.108	2.257
Occipital lobe, cuneus, BA 18	Left	−2	−91	6	2.074	2.216
(b) CRT						
Frontal lobe, sub-gyral	Right	40	15	25	3.94	4.458
Sub-lobar, caudate, caudate head	Right	10	13	−6	3.227	3.511
Medial frontal gyrus	Right	16	47	0	3.58	3.967
Frontal lobe, superior frontal gyrus, BA 11	Right	18	63	−13	3.024	3.258
Frontal lobe, sub-gyral	Right	28	43	13	3.562	3.943
Inferior frontal gyrus	Right	44	37	0	3.237	3.524
Frontal lobe, inferior frontal gyrus	Right	40	35	7	3.036	3.274
Occipital lobe, cuneus, BA 18	Right	2	−95	8	3.425	3.764
Frontal lobe, inferior frontal gyrus	Left	−36	31	8	3.374	3.698
Frontal lobe, sub-gyral	Left	−38	19	21	2.974	3.197
Frontal lobe, middle frontal gyrus	Left	−36	42	−9	2.96	3.18
Sub-lobar, caudate, caudate body	Left	−12	−1	15	2.611	2.764
Sub-lobar, caudate, caudate head	Left	−6	15	−6	2.282	2.385
Temporal lobe, superior temporal gyrus, BA 38	Right	46	14	−28	2.341	2.452
Temporal lobe, superior temporal gyrus	Right	48	−48	19	3.21	3.489
Temporal lobe, inferior temporal gyrus	Right	57	−26	−21	3.149	3.413
Temporal lobe, superior temporal gyrus	Right	50	−38	7	3.009	3.24
Midbrain, brainstem, red nucleus	Right	4	−20	−4	3.095	3.346
Temporal lobe, middle temporal gyrus	Left	−44	−66	11	3.159	3.425
Occipital lobe, middle occipital gyrus	Left	−48	−70	−5	2.141	2.226
Posterior lobe, declive	Right	42	−73	−18	3.088	3.337
Temporal lobe, fusiform gyrus, BA 37	Right	48	−44	−16	3.019	3.252
Occipital lobe, lingual gyrus, BA 18	Right	30	−70	−10	2.899	3.106

[*continued overleaf*

Table 2 *(cont.)*

Tailarach functional area specification	Hemisphere	x	y	z	Z score	*t* score
Superior temporal gyrus, BA 22	Left	−65	−19	5	3.079	3.326
Temporal lobe, inferior temporal gyrus	Left	−48	−5	−30	2.802	2.989
Temporal lobe, superior temporal gyrus	Left	−50	−37	7	2.698	2.866
Parietal lobe, inferior parietal lobule	Left	−46	−35	35	3.039	3.276
Occipital lobe, fusiform gyrus, BA 37	Left	−28	−47	−9	3.029	3.265
Posterior lobe, declive	Left	−40	−75	−21	3.003	3.233
Anterior lobe, culmen	Left	−34	−42	−25	2.989	3.215
Frontal lobe, middle frontal gyrus, BA 6	Left	−48	6	48	3.012	3.244
Frontal lobe, inferior frontal gyrus, BA 45	Left	−55	20	19	2.613	2.766
Frontal lobe, inferior frontal gyrus, BA 9	Left	−55	9	31	2.562	2.707
Posterior lobe, uvula	Right	14	−85	−24	3.012	3.244
Posterior lobe, tuber	Right	24	−81	−30	2.105	2.186
Frontal lobe, superior frontal gyrus, BA 8	Right	2	30	52	2.563	2.708
Parietal lobe, precuneus	Left	−12	−72	46	2.55	2.693
Occipital lobe, cuneus	Left	−10	−84	37	2.187	2.278
Frontal lobe, medial frontal gyrus	Left	−10	48	18	2.931	3.145
Frontal lobe, superior frontal gyrus	Left	−20	53	7	2.859	3.058
Frontal lobe, superior frontal gyrus, BA 9	Left	−4	56	30	2.84	3.035
Limbic lobe, cingulate gyrus, BA 24	Right	4	−14	34	2.901	3.108
Frontal lobe, medial frontal gyrus	Left	−8	−19	53	2.736	2.911
Frontal lobe, paracentral lobule, BA 31	Left	−8	−13	47	2.701	2.869
Middle temporal gyrus, BA 21	Left	−61	−58	5	2.88	3.083
Inferior temporal gyrus, BA 20	Right	50	−9	−31	2.864	3.064
Temporal lobe, fusiform gyrus, BA 20	Right	48	−21	−26	2.454	2.582
Parietal lobe, insula	Left	−46	−13	15	2.843	3.039
Frontal lobe, middle frontal gyrus, BA 6	Left	−24	−4	43	2.827	3.02
Parietal lobe, sub-gyral	Left	−30	−64	31	2.775	2.958
Parietal lobe, superior parietal lobule, BA 7	Left	−26	−52	43	2.077	2.154
Occipital lobe, cuneus	Left	−24	−79	19	2.774	2.956
Frontal lobe, inferior frontal gyrus, BA 47	Right	36	26	−15	2.754	2.932
Lingual gyrus	Right	22	−87	3	2.724	2.897
Occipital lobe, middle occipital gyrus, BA 18	Right	16	−87	15	2.606	2.759
Middle occipital gyrus, BA 18	Right	26	−97	3	2.327	2.436
Limbic lobe, cingulate gyrus	Left	−10	10	40	2.706	2.876
Parietal lobe, inferior parietal lobule	Right	44	−35	39	2.69	2.857
Frontal lobe, inferior frontal gyrus	Right	61	13	25	2.689	2.856
Temporal lobe, superior temporal gyrus	Left	−46	−50	12	2.649	2.808
Parietal lobe, precuneus	Right	18	−66	38	2.327	2.436
Occipital lobe, precuneus, BA 31	Right	16	−59	27	2.26	2.36
Frontal lobe, medial frontal gyrus, BA 6	Right	10	−21	49	2.548	2.69
Posterior lobe, cerebellar tonsil	Left	−6	−56	−38	2.538	2.679
Frontal lobe, medial frontal gyrus	Left	−10	52	−8	2.505	2.64
Parietal lobe, sub-gyral, BA 39	Right	32	−60	36	2.456	2.584
Parietal lobe, superior parietal lobule, BA 7	Right	34	−64	46	2.044	2.118
Sub-lobar, extra-nuclear	Left	−28	7	−10	2.453	2.58
Posterior lobe, declive	Left	−20	−59	−11	2.413	2.535
Anterior lobe, culmen	Left	−6	−57	−16	2.347	2.459
Posterior lobe, declive	Left	−22	−67	−15	2.216	2.311
Frontal lobe, superior frontal gyrus	Right	18	25	43	2.402	2.522
Anterior lobe, culmen	Left	−28	−57	−19	2.389	2.507
Fontal lobe, middle frontal gyrus	Right	57	2	40	2.365	2.48
Frontal lobe, superior frontal gyrus	Left	−34	60	−1	2.355	2.468
Sub-lobar, insula	Right	46	−13	17	2.345	2.457

Table 2 *(cont.)*

Tailarach functional area specification	Hemisphere	x	y	z	Z score	*t* score
Parietal lobe, inferior parietal lobule	Right	36	−42	54	2.342	2.454
Frontal lobe, superior frontal gyrus	Left	−24	42	22	2.341	2.452
Parietal lobe, precuneus	Right	2	−46	50	2.325	2.434
Posterior lobe, pyramis	Left	−18	−83	−29	2.314	2.421
Parietal lobe, precuneus, BA 7	Left	−8	−61	58	2.293	2.397
Frontal lobe, middle frontal gyrus, BA 8	Right	40	28	47	2.286	2.39
Limbic lobe, cingulate gyrus	Right	12	2	44	2.256	2.356
Posterior lobe, pyramis	Left	−26	−75	−30	2.249	2.348
Posterior lobe, declive	Left	−24	−75	−21	2.141	2.227
Occipital lobe, lingual gyrus	Left	−26	−88	−6	2.215	2.31
Parietal lobe, sub-gyral	Left	−30	−46	43	2.14	2.225
Sub-lobar, insula	Right	38	−7	8	2.14	2.225
Parietal lobe, inferior parietal lobule	Left	−65	−33	31	2.107	2.188
Frontal lobe, superior frontal gyrus	Right	12	52	25	2.052	2.127

The table presents Talairach functional area specification (Research Imaging Center, 2004) and coordinates, along with *Z* and *t* score statistics, for the maximum voxel score for each significant cluster. These areas can be directly compared to the PET images in Figure 2b (CPT) and Figure 3a (CRT). The values in the table indicate the original level of significance ranging from $p < 0.025$ ($Z > 2.28$) and in addition, those values at the more stringent $p < 0.01$ ($Z > 2.58$), $p < 0.002$ ($Z > 3.09$), $p < 0.001$ ($Z > 3.28$). BA, Brodmann area.

personality traits present at birth. Additionally, it is likely that other genetic factors contribute to susceptibility to nicotine. These results suggest that male and female subjects are differentially susceptible to nicotine based on the rigors imposed by certain tasks, and by implication, certain environments and social situations with attentional and retaliatory demands. Our results may be relevant to understanding the gender differences in smoking behaviours in different environments.

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Statement of Interest

None.

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