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Nicotine Alters Food–Cue Reactivity via Networks Extending From the Hypothalamus

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Obesity and smoking constitute two of the main causes of preventable deaths in the developed countries today. Many smokers motivate consumption as a means to control their body weight because smoking cessation increases the risk to gain weight. Although it is well established that nicotine reduces feeding in animals and that smoking is associated with reduced body weight in quasi-experimental studies of humans, acute nicotine effects are mixed and little is known about the brain networks supporting these effects. Thus, we investigated 26 normal-weighted never-smokers who received either nicotine (2 mg) or placebo gums following a double-blinded randomized cross-over design. We used functional magnetic resonance imaging (fMRI) to investigate reactivity to palatable food cues after both overnight fasting and following a standardized caloric intake (75 g oral glucose tolerance test (OGTT)). Participants viewed food or low-level control pictures in a block design and rated their current appetite after each block. Nicotine had a small- to medium-sized effect on subjective appetite and significantly altered food–cue reactivity in a region sensitive to caloric intake that extended from the right hypothalamus to the basal ganglia. During placebo sessions, the OGTT reduced functional coupling of this region with a 'salience network' (ie, amygdala, ventromedial prefrontal cortex) in processing of food pictures. Furthermore, nicotine reduced coupling with the nucleus accumbens and the OGTT reduced coupling with an 'interoceptive network' (ie, insula, operculum) instead. We conclude that locally restricted acute effects of nicotine in the hypothalamic area have profound effects on food-processing networks.
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INTRODUCTION

Securing sufficient quantities of food to meet energy-expenditure demands is the most vital task for survival of any organism. Not surprisingly though, human brain evolution was strongly driven by the need to supply food for thought. Literally, encephalization was fostered by 'clever foraging' techniques (ie, hunting prey; Striedter, 2005) and brain circuits evolved to prioritize behavior accordingly. On the one hand, the central melanocortin system, primarily routed in the hypothalamus and brain stem (Cone, 2005), is responsible for monitoring homeostatic needs. On the other hand, brain reward systems control learning and modulate attention and effort towards obtaining palatable food. Notably, the mesolimbic dopaminergic system encoding this incentive value receives hormonal projections; for example, the nucleus accumbens (NAcc) is innervated by insulin receptors and ghrelin, which is the only circulating peptide known to increase appetite, enhances dopaminergic signaling in the ventral tegmental area (VTA; cf Kenny, 2011). Hence, homeostatic signals have the potential to enhance hedonic properties of food cues (Kroemer *et al*, 2012a).

The etiology of obesity and drug addiction is associated with common cellular and molecular mechanisms in both homeostatic and hedonic brain networks (Kenny, 2011). Obesity, alcohol and tobacco consumption are among the main causes of preventable deaths in the developed countries today (Danaei *et al*, 2009). Intriguingly, many smokers motivate their consumption as a means to control body weight and apprehensions to gain weight after smoking cessation are a major reason not to quit. Therefore, it is crucial to understand interactions of nicotine and food consumption in humans, because common biological mechanisms strongly suggest that the treatment of a singular pathological state may support the manifestation of the other.

Food Reward: Cue Reactivity and Consumption

Pictures that depict usage of desirable substances such as drugs are well known to elicit strong responses in hedonic circuits that predict craving and risk for relapse after cessation (Grüsser *et al*, 2004). Palatable food pictures elicit

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a neural response in regions such as the fusiform gyrus, the insula, the orbitofrontal cortex (OFC), and the amygdala, with the latter two regions being more responsive in a hungry state (van der Laan *et al*, 2011) and there is substantial overlap with reactivity to smoking cues (Tang *et al*, 2012). Energy content of the pictures, corresponding closely to perceived palatability, is represented in a cluster extending from the right hypothalamus to the ventral striatum (van der Laan et al, 2011) that additionally integrates information of energy stores to bias food–cue reactivity accordingly (Kroemer *et al*, 2012b). To estimate this effect, a controlled amount of calories can be administered after overnight fasting using, for example, an oral glucose tolerance test (OGTT). The glucose solution contains 300 kcal, is relatively independent from context and individual factors such as palatability, and it has been demonstrated to modulate the BOLD signal of the hypothalamus in a dose-dependent relationship (cf Kroemer *et al*, 2012b). Furthermore, food–cue reactivity in the insula, fusiform gyrus, and the ventral striatum predicted long-term body-weight change after participating in a weight-loss program (Murdaugh *et al*, 2012). Whereas higher reactivity in taste-related regions (Stice *et al*, 2008b) and oral somatosensory regions was reported in obesity (Stice *et al*, 2009), reduced reactivity in somatosensory regions was implicated in anorexia (while reactivity in attentional regions was increased during fasting; Santel *et al*, 2006). In addition, attenuated dopamine signaling is reflected in reduced food–cue reactivity in the dorsal striatum and increases risks for overconsumption and obesity (Stice *et al*, 2008a).

Nicotine Effects on Body Weight

Smoking cessation is consistently associated with higher risks to gain weight (Filozof *et al*, 2004) and concerns are negatively associated with intentions to quit and chances for successful cessation (Meyers *et al*, 1997). However, estimates of annual weight gain after successful smoking cessation differ substantially (0.5–3 kg; eg, O'Hara *et al*, 1998; Munafo *et al*, 2009; Travier *et al*, 2012; Williamson *et al*, 1991), with the strongest increase in weight recorded during the first year. However, there seems to be no absolute (Williamson *et al*, 1991) or relative difference (Travier *et al*, 2012) in weight gain to non-smokers after successful smoking cessation. Critically, the risk to gain weight increases substantially for smokers with overweight or obesity (Lycett *et al*, 2011).

On the one hand, it is not well supported today that heightened metabolism is a decisive component in nicotine's effects on body weight (see Supplementary Information). On the other hand, numerous animal studies showed that nicotine reduces food intake (eg, Bellinger *et al*, 2010; Grunberg et al, 1988; Wellman *et al*, 2005; Yang *et al*, 1999). Specifically, nicotine's interactions with signaling pathways routed in the hypothalamus were implied in these anorexic effects (Li *et al*, 2000; Mineur *et al*, 2011). Whereas results show that expression of neuropeptide Y in rats (Li *et al*, 2000) and activation of pro-opiomelanocortin (POMC) neurons in mice (Mineur *et al*, 2011) critically contribute to nicotine's effects on food intake in rodents (see Supplementary Information), we are not aware of any study in humans that attempted to test this interaction using a pharmacological challenge. Furthermore, little is known about the complex cascade of regulatory responses that are triggered by nicotine's effects on hypothalamic signaling in humans.

Thus, we hypothesized that nicotine alters (a) processing of food pictures in the hypothalamus and (b) functional coupling of this cluster to the NAcc. Regarding caloric intake, we expected nicotine to alter functional coupling of the hypothalamus to brain networks supporting processing of incentive salience (ie, hedonic hunger) and interoception (ie, homeostatic hunger).

MATERIALS AND METHODS

Participants

This study is based on a sample reported in detail in a previous study (Kroemer *et al*, 2012b; see Supplementary Information). We included 26 right-handed healthy never-smokers (13 male) for the following analyses. Never-smokers were defined as current non-smokers who smoked <20 cigarettes in their lifetime. Their mean age was 24.4 ± 3.4 years and they were within the range of normal weight (ie, $18.5 \leqslant BMI_i \leqslant 24.9\,kg/m^2$; $M_{BMI} = 21.1 \pm 2.0\,kg/m^2$). The study was approved by the institutional review boards of the Faculty of Medicine Mannheim and informed consent was obtained from all participants.

Procedure

Participants arrived between 0730 and 0900 hours. They were allowed to take the last meal at 2200 hours the day before the experiment. Ten minutes after their arrival, the first blood sample was collected and participants were instructed to chew the nicotine (2 mg Nicorette) *vs* placebo chewing gum for 30 min. After they finished chewing, a second blood sample was collected to assess nicotine levels. The stimulus set consisted of 120 food and 120 low-level control pictures. Food stimuli were selected based on high-palatability ratings in an evaluation study and control pictures were created by scrambling them to match in intensity, contrast, and brightness. The fMRI session consisted of two 15-min runs separated by a break to administer the OGTT. In each run, pictures of both categories were presented in a block design with 12 food and control blocks in a pseudorandom order to ensure that three blocks in a row never contained the same stimulus category. Each block consisted of five pictures. Every picture was presented for 4 s via MR-compatible goggles using MRI Audio/Video Systems (Resonance Technology, Northridge, CA).

After presenting the last picture of a block, a fixation cross appeared for 500 ms. Thereafter, a rating slide with the statement: 'I feel like eating now' was presented. Participants had to indicate how much they felt like eating at the moment on a visual analog scale with the end points: 'totally disagree' *vs* 'totally agree' by moving an MR-compatible response pad with their right hand. A fixation cross followed and after a total time of 15.5 s, a new block started. After the first run, participants were removed from the scanner and drank a solution containing the equivalent of

75 g of glucose (defined by a 300 ml mixture of mono- and oligosaccharides; ACCU-CHEKDextro OG-T; Roche) on the scanner bed. Five minutes after they started drinking, participants continued with the second fMRI run, which consisted of new pictures presented in the same design. Presentation software (Version 9.90; Neurobehavioral Systems, Albany, CA) was used to present pictures and collect data. Further blood samples were collected but not used for following analyses (see Supplementary Information).

Data Acquisition and Analysis

Images were acquired with a 3 T whole-body MRI scanner (TRIO; Siemens, Erlangen, Germany) equipped with a standard head coil. First-level contrast images (see Supplementary Information) food–control pictures were entered into a second-level analysis comprising a repeated-measures ANOVA. The model consisted of the two-level within-subject factor caloric load (food *vs* control before and food *vs* control after OGTT) and the two-level within-subject factor nicotine (2 mg *vs* placebo). Entering order as a covariate of no interest did not significantly alter the results, so we will report the more parsimonious model only.

We expected nicotine administration to reduce food–cue reactivity, specifically in the hypothalamus and during the fasting state. Thus, we used a small-volume correction using spheres of 5 mm radii around the hypothalamic center MNI coordinates of $\pm 8/-4/-4$ (eg, http://fmri.wfubmc.edu/software/PickAtlas) to weight anatomical size and precision of functional localization. In addition, we explored whole-brain differences using an uncorrected $p<0.001$ with a minimal cluster size $k=20$ as primary statistical threshold because it is sufficiently balanced with regard to type-I and type-II errors (Lieberman and Cunningham, 2009). For analysis of behavioral data, we used a threshold of $p<0.05$ (two-tailed). Hedge's g was calculated as an unbiased measure of effect size based on a pooled estimate of SD uncorrected for correlation of repeated measures (ie, a between-subjects t-test) as recommended by Dunlop *et al.* (1996). For further statistical analyses, we used HLM 7 and SPSS 19.

PPI Analysis

Changes in functional coupling between the hypothalamus and other brain areas were estimated using PPI analysis (Friston *et al*, 1997). This approach searches for brain-wide correlations in a seed region under a certain context-dependent condition. PPI analysis has been shown to be more sensitive than simple correlations to extract inter-regional connections between brain regions (Kim and Horwitz, 2008).

For each subject, a GLM model is built containing three regressors. The first (physiological) regressor is the first eigenvariate of the time series of a volume of interest (VOI); specifically, this VOI corresponded to a 5 mm sphere centered at the peak voxel (10/0/−4) within the *a priori* ROI analysis of the hypothalamus. The second regressor is given by the experimental contrast of interest (nicotine *vs* placebo, fasting *vs* after caloric load). The third regressor corresponds to an interaction regressor psychological factor × physiological factor. Contrast images from the first-level analysis were included in second-level random-effects analyses to determine which brain areas increased or decreased their connectivity with the seed region under the experimental condition. In addition to the whole-brain threshold, in the figures in the Results section, we show voxels that survive the more liberal $p<0.005$ uncorrected, to enhance visualization and to facilitate comparisons of the modulated networks. In summary, we conducted eight first-level statistic PPI's (nicotine *vs* placebo; food *vs* control pictures; fasting *vs* after caloric load) and one repeated-measures ANOVA at second level. Because we are, to the best of our knowledge, the first to investigate the regulatory response of nicotine, our analyses will focus on well-known food-processing regions while being exploratory in the sense that we report whole-brain findings to reduce risks of false negatives to future research.

RESULTS

Nicotine Administration and Blood Plasma Levels of Nicotine and Cotinine

After administration of the nicotine gum (ie, 25 min after they started chewing), participants had a mean blood plasma level of 3.50 ng/ml (SD = 0.95) and a mean cotinine level of 3.16 ng/ml (SD = 3.67). Notably, nicotine levels were not significantly correlated with sex ($r=-0.15$, $p=0.45$) or BMI ($r=-0.32$, $p=0.11$) and, thus, may provide a more sensitive measure of effective nicotine uptake relatively independent of metabolism (for effectiveness of blinding, see Supplementary Information).

Effect of Nicotine on Subjective Appetite

We conducted a repeated-measures ANOVA consisting of the three two-level factors picture (food *vs* control), caloric load (fasting *vs* after caloric load), and nicotine (2 mg *vs* placebo). As expected, subjective appetite ratings were higher following food *vs* control picture blocks (main effect of picture, $F(1,25)=38.4$, $p<0.001$, $\eta_p^2=0.61$) and they decreased after caloric load (main effect of caloric load, $F(1,25)=15.8$, $p=0.001$, $\eta_p^2=0.37$). However, there was no main effect of nicotine, $F(1,25)=0.8$, $p=0.38$, $\eta_p^2=0.03$. In addition, the caloric load reduced the difference in subjective appetite between food and control blocks (picture × caloric load, $F(1,25)=9.2$, $p=0.006$, $\eta_p^2=0.27$). Whereas the picture × nicotine interaction was not significant, $F(1,25)=0.2$, $p=0.63$, $\eta_p^2=0.01$, nicotine tended to reduce fasting appetite ratings more than ratings after caloric-load (caloric load × nicotine, $F(1,25)=3.5$, $p=0.072$, $\eta_p^2=0.12$). Although nicotine effects were not significant, the effect-size estimates (Hedge's $g_{FOOD}=0.33$; Hedge's $g_{CONTROL}=0.38$) point to a small negative effect on subjective appetite during the fasting state (Supplementary Figure S1 and see Supplementary Information). Nevertheless, accounting for differences in blood plasma levels of nicotine yielded a significant correlation with differences in subjective appetite ratings during fasting state between placebo and nicotine sessions ($r=0.40$, $p=0.046$).

Because mean appetite ratings do not capture changes over blocks, we also investigated effects of nicotine levels on

the slopes of cue-induced appetite (using restricted maximum-likelihood estimation) within the nicotine session. The higher the nicotine level, the lower was the slope of appetite ratings after the caloric load ($r = -0.42$, $p = 0.035$), but not significantly during fasting (see Supplementary Information). As a proof of concept, nicotine levels were also correlated with initial appetite ratings (ie, the intercept) averaged over conditions ($r = -0.40$, $p = 0.042$). To summarize, nicotine had a small- to medium-sized effect on mean subjective appetite ratings during fasting state and blood plasma nicotine levels correlated negatively with slopes for appetite ratings over blocks of the food–cue task after a standardized caloric intake.

Main Effect of Glucose Administration on Food–Cue Reactivity

Averaging over both sessions, administration of the caloric load reduced the contrast food–control pictures in the dorsolateral prefrontal cortex ($t_{max} = 3.86$, $k = 65$, 4/54/20; exploratory whole brain) and the posterior cingulate gyrus ($t_{max} = 3.84$, $k = 43$, 12/−36/14; exploratory whole brain). In addition, the contrast increased in the dorsal and ventral stream, post- and precentral gyri, and the dorsolateral prefrontal cortex (Supplementary Table S1).

Effect of Nicotine on Food–Cue Reactivity

Administration of nicotine reduced the contrast food–control pictures in the periaqueductal gray ($t_{max} = 3.51$, $k = 24$, 4/−34/−8; exploratory whole brain). Whereas there was no significant main effect of nicotine on food–cue reactivity in the hypothalamus over both sessions, nicotine significantly reduced the contrast food–control pictures during the fasting state ($t_{max} = 3.14$, $p_{FWE\_corr} = 0.02$). Consequentially, there was a significant positive interaction (ie, food–cue reactivity decreased after the caloric load during placebo, but tended to increase during nicotine sessions) in the right hypothalamus ROI ($t_{max} = 4.21$, $p_{FWE\_corr} = 0.001$; Figure 1). In addition, there was another cluster in the anterior cingulate gyrus ($t_{max} = 4.24$, $k = 35$, 10/20/18) showing this positive interaction that survived our exploratory whole-brain threshold.

PPI Analyses

In accordance with our hypothesis, nicotine interacted with the contrast between food and low-level control pictures in the hypothalamus. Thus, we computed a PPI analysis using a sphere of 5 mm radius surrounding the peak interaction voxel (10/0/−4) within the right hypothalamus. Notably, nicotine reduced functional coupling during presentation of food *vs* control pictures in the left ($t_{max} = 3.93$; $p_{SVC} = 0.004$; −16/12/−8) and right NAcc ($t_{max} = 3.10$; $p_{uncor} = 0.001$; $p_{SVC} = 0.051$; 10/14/−8; see Figure 2) for both runs. Another cluster in the cerebellum ($t_{max} = 3.53$; $k = 31$; −10/−68/−26) survived the exploratory whole-brain threshold.

Effects of the standardized caloric load on differences in functional coupling between food and control pictures demonstrated which networks were differentially affected during placebo and nicotine sessions (Figure 3). During placebo sessions, the OGTT reduced functional coupling of the hypothalamic cluster with a basal network incorporating paralimbic (parahippocampal cortex; anterior cingulate cortex), limbic (amygdala; hippocampus), bottom-up visual processing (fusiform gyrus), and medial orbitofrontal regions (BA 10; see Supplementary Table S2). During nicotine sessions however, the OGTT reduced functional coupling in a more superior network involving the primary and secondary taste-processing regions (insulae; rolandic operculum; lateral OFC), top-down visual processing (pulvinar), and selection, initiation (dorsal striatum), motor execution (precentral gyrus), and inhibition of actions (pars triangularis; see Supplementary Table S2). Despite notable overlap in the left amygdala, the networks are strikingly distinct so that direct comparisons between placebo and nicotine sessions yield essentially the same results (see Table 1 and Supplementary Figure S2).

As a proof of concept, we correlated blood plasma levels of nicotine with functional coupling of the hypothalamus. Notably, the higher the levels of nicotine, the stronger was

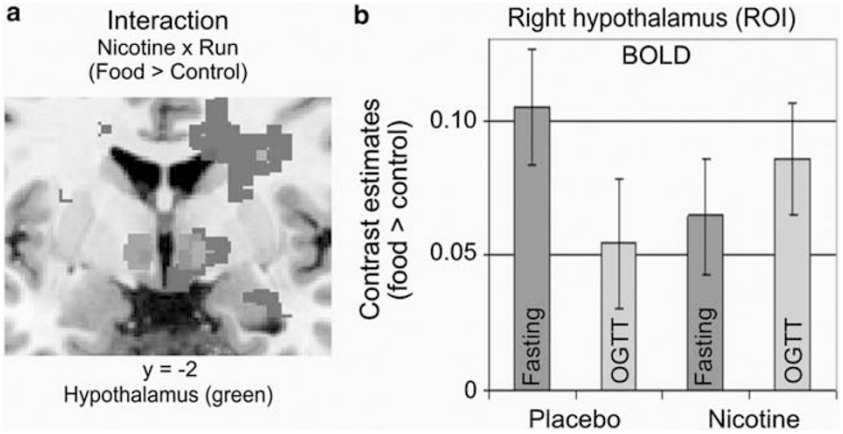

Figure 1 Effects of the standardized caloric intake (oral glucose tolerance test (OGTT)) and the administration of nicotine on the blood oxygen level dependence (BOLD) response in the *a priori* region of interest (ROI) hypothalamus. (a) The image is thresholded at $p < 0.05$, uncorrected (red), and $p < 0.05$, small-volume corrected (yellow). (b) Extracted contrast estimates (food–control) from the right hypothalamus during fasting state (dark gray) and after the standardized caloric intake (light gray). Error bars represent ± 1 SEM. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

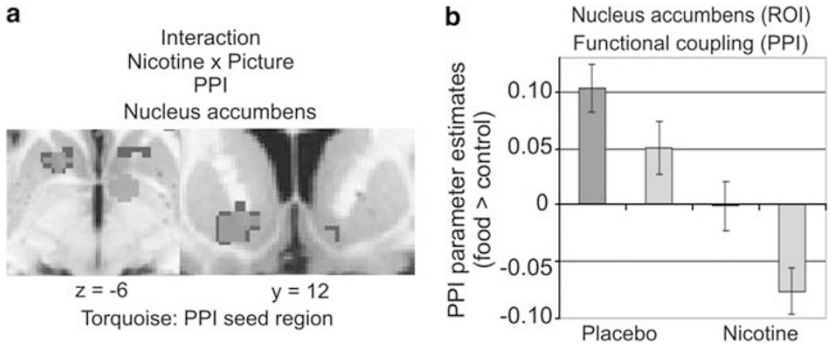

Figure 2 Interaction of nicotine administration with functional coupling of the right hypothalamic cluster with the nucleus accumbens during presentation of food *vs* control picture blocks. (a) The images depict the hypothesized interaction that nicotine reduces functional coupling and they are thresholded at $p<0.005$, uncorrected (red), and $p<0.001$, uncorrected (yellow). Note that slice numbers correspond to the respective MNI (Montreal Neurological Institute) coordinate. (b) Extracted psychophysiological interaction (PPI) parameter estimates (food–control) from the PPI using the right hypothalamic cluster as a seed region and an anatomical mask of the nucleus accumbens. Bars depict parameter estimates during fasting state (dark gray) and after the standardized caloric intake (light gray). Error bars represent ± 1 SEM. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

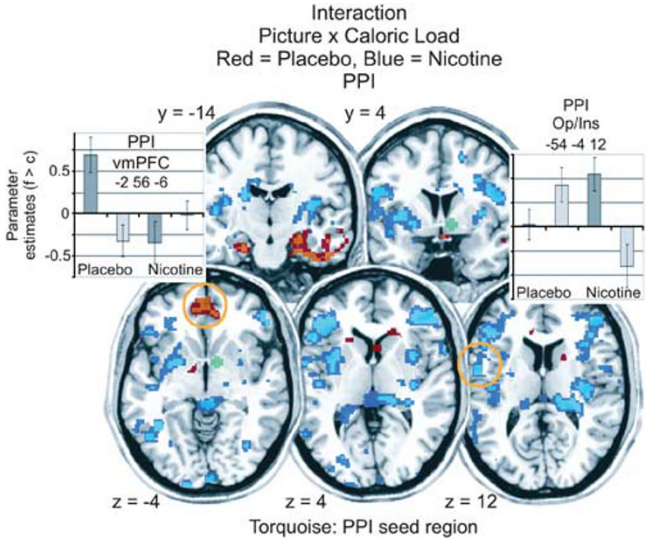

Figure 3 The images depict the hypothesized interaction that the standardized caloric intake reduces functional coupling during food–picture blocks compared with control–picture blocks. Images are thresholded at $p<0.005$, uncorrected (red = placebo; blue = nicotine), and $p<0.001$, uncorrected (yellow = placebo; light-blue = nicotine). Bar charts (dark gray = fasting; light gray = after caloric load) purely illustrate direction of the differences in functional coupling to ventromedial prefrontal cortex (vmPFC) and operculum/insula (Op/Ins) and represent extracted parameter estimates (± 1 SEM) from the peak voxel of the clusters highlighted by a yellow circle. Note that slice numbers correspond to the respective MNI (Montreal Neurological Institute) coordinate.

the coupling of the hypothalamic cluster with amygdalae, hippocampi and parahippocampal gyri in both hemispheres (Figure 4 and Supplementary Table S3). This indicates that nicotine potentially alters functional coupling with subcortical brain regions in a dose–response relationship.

DISCUSSION

To summarize, nicotine affected food–cue reactivity as indicated by reduced subjective appetite and a reduced contrast between food and control pictures in the hypothalamus during the fasting state. This is in line with the findings by Mineur *et al* (2011), who demonstrated that POMC neurons in the hypothalamus are necessary and sufficient to produce the anorexic effects of nicotine in rodents. Nevertheless, our study extends these results to a human population and sheds light on the complex interaction effects of a spatially restricted effect in the hypothalamic area with other key regions in food-processing networks, which hints at how nicotine may affect behavior.

The hypothalamus functionally integrates endocrinological and neural information to potentially provide feedback to the organism (Shin *et al*, 2009; Horvath *et al*, 2001). It expresses $\alpha 3\beta 4$ nicotinic acetylcholine receptors on POMC neurons providing the neuromolecular basis to alter this feedback. We found that nicotine reduced functional coupling of the hypothalamic cluster with the NAcc during food–picture blocks. Converging evidence suggests that a region extending from the hypothalamus to the ventral striatum mediates biasing of food–cue reactivity based on energy-content information (Cornier *et al*, 2007; Farooqi *et al*, 2007; van der Laan *et al*, 2011). Intriguingly, the melanocortin system is known to project to the ventral striatum mediating dopamine release in the NAcc (Lindblom *et al*, 2001), which makes it reasonable to hypothesize that these neural connections represent reduced coupling of the homeostatic- and the hedonic-hunger systems.

This interpretation is substantiated by the distinct networks that are affected by the administration of a standardized caloric load. These networks are well known to serve complementary roles in appetitive behavior (van der Laan *et al*, 2011). First, the lateral hypothalamic area is known to mediate dopaminergic neurons of the VTA (Fadel and Deutch, 2002; You *et al*, 2001) and the amygdala and the ventromedial prefrontal cortex are strongly innervated by dopaminergic projections (Haber and Knutson, 2009). Both regions are thought to be involved in attributing salience to environmental cues and they are modulated by hunger (Siep *et al*, 2009). Consequentially, reduced functional coupling during placebo sessions following caloric intake may reflect the reduction of an elevated hedonic response to food pictures due to the prior fasting state.

Table 1 PPI: Positive Interaction of Run (fasting–post-caloric load) and Picture (food–control) with Nicotine Administration

Region	Side	*k*	MNI coordinates			t_{max}
			x	*y*	*z*	
Placebo > nicotine						
Parahippocampal gyrus (BA 35)	R	27	30	−8	−32	3.58
Medial frontal gyrus (BA 10)	L	46	−2	56	−4	3.57
Nicotine > placebo						
Cingulate gyrus (BA 24)	L	211	−12	−4	34	4.58
Caudate body, thalamus (ventral lateral nucleus)	L		−22	−16	22	4.15
Insula (BA 13)	L		−40	−16	26	3.83
Inferior temporal gyrus (BA 37)	L	67	−42	−44	−14	4.29
Inferior frontal gyrus (pars opercularis, BA 44)	R	72	50	2	20	4.10
Inferior frontal gyrus (pars triangularis, BA 45)	L	92	−48	20	6	4.05
Inferior frontal gyrus (pars opercularis, BA 44)	L		−46	10	10	3.55
Rolandic operculum, precentral gyrus (BA 6)	L	88	−54	−4	12	3.85
Thalamus (pulvinar)	R	27	26	−30	12	3.80
Precentral gyrus (BA 9)	R	40	30	2	36	3.65
Caudate body	R	24	20	−4	24	3.61
Cingulate gyrus (BA 24)	R	22	14	4	38	3.46

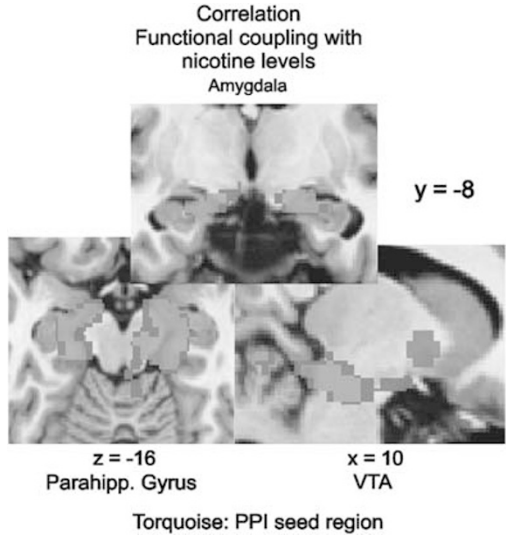

Figure 4 Images are thresholded at $p < 0.005$, uncorrected (red), and $p < 0.001$, uncorrected (yellow). Note that slice numbers correspond to the respective MNI (Montreal Neurological Institute) coordinate. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

During nicotine sessions, this homeostatic feedback mechanism of the hypothalamic cluster is decoupled from the hedonic-hunger network as reflected by attenuated food–cue reactivity and reduced functional coupling with the NAcc during food-picture blocks. Second, the caloric intake was followed by reduced functional coupling with a more superior network that primarily involved interoceptive regions. The insula and the operculum are well known to contain the primary gustatory area representing sensations of taste (Augustine, 1996; Small, 2010; Small *et al*, 1999) and both regions are responsive to pictures of palatable food (Simmons *et al*, 2005). In addition, the effect in the cingulate gyrus may be due to strong connections with insular regions potentially subserving evaluative functions to select and prepare for future actions (Medford and Critchley, 2010). Reduced functional coupling with the precentral gyrus during nicotine sessions roughly corresponds to the somatotopic regions of tongue and lips (Meier *et al*, 2008). The pars triangularis of the inferior frontal gyrus is thought to be involved in inhibition of go responses, for example, during performance of the stop-signal task (Aron *et al*, 2003).

In a recent study by Brooks *et al* (2011), women suffering from bulimia nervosa showed stronger activation than women suffering from anorexia nervosa in similar regions of the somatosensory system including the body of the caudate as well. The authors suggested that although both groups apply cognitive–control strategies, increased activation in the somatosensory system might impinge on exerting control over food consumption. Consequentially, decreased functional coupling with the hypothalamus after caloric intake during nicotine sessions might facilitate cognitive control and there is considerable evidence of higher than expected comorbidity of smoking with bulimia nervosa as part of a self-medication strategy (Bulik *et al*, 1992; Welch and Fairburn, 1998). Taken together, these network effects might help to explain why nicotine decreases meal size in rodents on a standard chow diet on the one hand (Bellinger *et al*, 2010), whereas it reduces the number of meals as well on a more energy-dense high-fat diet (Wellman *et al*, 2005). Our data suggest that nicotine decreases hedonic hunger during fasting state (which would delay meal initiation particularly in being confronted with palatable food options) and that the caloric intake affected

functional coupling with an interoceptive somatosensory network that may reduce homeostatic hunger more efficiently (which would reduce meal size and may account for less cue-induced appetite the higher the nicotine levels were).

Future studies will need to address limitations of the current design. First, nicotine effects on subjective appetite ratings were small to moderate only. This might be attributable to a single and comparatively low dose of nicotine. Second, never-smokers may respond differently to nicotine than smokers due to self-selection effects after initial drug consumption (ie, with nausea; see Supplementary Information). These issues might be resolved, for instance, by studying occasional smokers because they do not experience withdrawal and have developed a higher tolerance to negative side effects or investigating quitting smokers in a pre–post design. Ideally, the design would be extended by administering different nicotine doses following a within-subject design to assess if there is a gradual or discrete difference in the network effects after caloric intake reported here. Moreover, variations in nicotine levels may reduce power to detect effects so that limiting variance in terms of pharmacodynamics is strongly desirable. Third, the spatial resolution of common fMRI whole-brain protocols does not truly allow for sharp distinctions between activation of the hypothalamus and neighboring brain regions such as the medial globus pallidus. Thus, we cannot provide enough evidence that it was indeed *only* signaling in the hypothalamus that was affected by nicotine administration. Nevertheless, studies in rodents strikingly argue in favor of a critical role of the hypothalamus and the connectivity results are in accordance with the current knowledge of hypothalamic networks.

We conclude that nicotine alters food–cue reactivity in a hypothalamic cluster that was responsive to caloric intake during placebo sessions. This may represent the anorexic potential of nicotine to alter hypothalamic projections and decouple homeostatic feedback information from the hedonic-hunger network effectively reducing incentive salience of food-reward cues. On the basis of these findings, future smoking-cessation therapies should extend stimulus-management strategies to food cues to reduce potentially the risk of weight gain after nicotine deprivation.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)