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Cognitive and hormonal regulation of appetite for food presented in the olfactory and visual modalities ☆

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ABSTRACT

The ability to regulate appetite is essential to avoid food over-consumption. The desire for a particular food can be triggered by its odor before it is even seen. Using fMRI, we identify the neural systems modulated by cognitive regulation when experiencing appetizing food stimuli presented in both olfactory and visual modalities, while being hungry. Regulatory instruction modulated bids for food items and inhalation patterns. Distinct brain regions were observed for up and down appetite-regulation, respectively the dorsomedial prefrontal cortex (dmPFC) and dorsolateral PFC. Food valuation engaged the ventromedial PFC and bilateral striatum. Furthermore, we identified a neurobiological marker for successful appetite upregulation. Individuals with higher blood levels of ghrelin were better at exercising up-regulation, and engaged the dmPFC more. These findings characterize the neural circuitry regulating food consumption within the healthy population and highlight how cognitive regulation modulates olfactomotor measures of olfaction.

1. Introduction

Obesity represents an increasing public health challenge (Flegal et al., 2016; Gallus et al., 2015; Sturm et al., 2013). There is a crucial need to understand the neurocomputational mechanisms underlying the regulation of food consumption, especially in a context of overexposure to food stimuli. Appetite, the desire to consume food, can be stimulated by visual stimuli, (tempting pictures or displays of food in shop windows), olfactory cues, (delicious smells), and the levels of hormones that signal hunger and satiety. Food consumption may also be regulated through the implementation of strategies, known as cognitive regulation. These strategies use attention, language and executive control to modulate the value people attribute to features of visual stimuli (Galsworthy-Francis and Allan, 2014; Siep et al., 2012; Yokum and Stice, 2013). Cognitive regulation thus serves as an important strategy by which the brain can control food craving.

Most of our knowledge about the neurobiological mechanisms underlying cognitive regulation of anticipated food stimuli is derived from fMRI studies using food images only (Hutcherson et al., 2012; Inui et al., 2004; Kober et al., 2010). These studies reported that presentation of visual food-cues engages brain regions associated with reward and valuation, the bilateral striatum and the ventromedial prefrontal cortex. Accumulated evidence indicate that the lateral prefrontal cortex (lPFC) plays a key role in modulating food cue induced signals by cognitive regulation strategies (Hollmann et al., 2012; Hutcherson et al., 2012b; Kober et al., 2010; Siep et al., 2012; Yokum and Stice, 2013 Schmidt et al., 2018). Early studies reported that the lPFC supports cognitive regulation by acting on value signals encoded in the ventromedial PFC (vmPFC) (Hare et al., 2009; Kober et al., 2010, Hutcherson et al., 2012b). However, a recent study found that the vmPFC activity may be insensitive to regulatory mechanisms during cognitive regulation (Tusche and Hutcherson, 2018), suggesting that cognitive regulation may act upstream of the integrated value signal by modulating specific attributes of value (Inzlicht et al., 2016).

Little is known about the neurobiological mechanisms underlying appetite regulation of food stimuli presented in a bimodal, realistic manner, such as when visual cues and food odors are combined. Food odors are potent signals for triggering appetite (Fine and Riera, 2019). For example, the smell of croissants wafting from a patisserie, can trigger a

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strong desire for this food in the absence of any visual cue. Food odors presented in the anticipatory phase of eating increase appetite compared with a no-odor condition (Ramaekers et al., 2014; Zoon et al., 2016), and internal state of hunger and satiety modulates olfactory exploratory behavior such as sniffing and breathing patterns (Prescott et al., 2010). However, it is unknown whether voluntary cognitive regulation also modulates measures of olfactomotor behavior (such as sniff duration or amplitude…). We hypothesize that voluntary cognitive regulation increases or decreases these measures (respectively for an upward regulation and downward regulation).

Parallels may exist between the neural mechanisms engaged in cognitive strategies used for emotion regulation and for the regulation of appetite (Buhle et al., 2014; Kober et al., 2010). Both types of regulatory mechanisms may engage common brain regions, such as the dorsolateral PFC (dlPFC) for down-regulation (Frank et al., 2014) and the anterior medial part of the PFC for up-regulation (Ochsner et al., 2004). A recent study also revealed increased dlPFC activity to visual food stimuli correlating with down-regulation of appetite for a particular food item after a bitter-taste (Wabnegger et al., 2018). We therefore expected that the lateral PFC may play a role in down-regulating food craving whereas the medial part of the PFC may support up-regulation of appetite for food stimuli presented in a realistic paradigm including olfactory and visual stimuli.

Endocrine influences on olfactory perception have been demonstrated (Sun et al., 2016; Tong et al., 2011). For example, ghrelin, body mass index (BMI) and feeding state (hungry vs sated) interact to influence odor intensity perception (Sun et al., 2016). Moreover, peripheral ghrelin infusion increases sniff magnitude in healthy humans (Tong et al., 2011). Homeostatic peptide hormones such as ghrelin, produced in the gastrointestinal tract convey energy balance information to the brain that affect food intake and act as an orexigenic hormone under hunger state. Ghrelin acts both on the homeostatic hypothalamic-brainstem circuits that regulate energy balance and on systems involved in reward and motivation (Mason et al., 2013; Perello and Dickson, 2015). High levels of ghrelin, either due to ghrelin injection or fasting, increase motivation for food rewards and modulate the reward system (Abizaid et al., 2006; Han et al., 2018; Karra et al., 2013; Kroemer et al., 2013; Shirazi et al., 2013). Ghrelin injection in sated participants leads to increased activity within the orbitofrontal cortex and correlates with higher self-rated hunger ratings following food pictures (Malik et al., 2008). Taken together these results suggest a link between ghrelin level, olfactory stimuli and appetite self-regulation.

In contrast, the anorexigenic properties of leptin lead to reduced food intake and motivation to attain rewards (Bruijnzeel et al., 2011; Hommel et al., 2006; Shen et al., 2016). Leptin injection modulates olfactomotor perception in rats (Julliard et al., 2007). However, in humans, leptin effects on olfaction have been shown to be less significant (Uygun et al., 2019). There are clear interactions between ghrelin/leptin levels and food motivated behaviors. However, no study has yet investigated the links between ghrelin/leptin levels and voluntary regulation of food stimuli presented in the visual and olfactory domains. We predicted to find a positive correlation between the peripheral ghrelin level and the BOLD signal of prefrontal areas involved in up-regulating appetite.

Here, we used fMRI to investigate the neural processes involved in appetite regulation during successive presentation of food odor and image. Healthy hungry participants made hypothetical food purchase decisions under a Natural control condition and two cognitive regulation conditions after exposure to food odors followed by corresponding food pictures. We addressed the effects of cognitive regulation on: (1) olfactomotor parameters of food odors; (2) subjective evaluation of food, as assessed by willingness to pay; (3) brain activity, investigating whether distinct or common PFC areas support up- and down-regulation of food items. Moreover, we investigated the influence of the appetite regulating hormones, ghrelin and leptin on behavior and brain activity.

2. Methods

2.1. Participants

Twenty-five healthy volunteers (12 females, 13 males; age range 18-33 years; and mean age (M) 22.45 ± (SEM) 3.88) were recruited through a mailing list from the University of Claude Bernard Lyon 1. All participants had a normal Body Mass Index (BMI) (mean (M) 21.74 ± (SEM) 0.36) and were food deprived for at least twelve hours before the beginning of the experiment. For inclusion in the study, participants were required to follow the following criteria: French-speaking, right-handed, no current medical treatment, no history of neurological or psychiatric disorders and no auditory, olfactory or visual deficits. Furthermore, volunteers were screened for general MRI contra-indications. A physician conducted medical examinations concerning inclusion criteria such as physical and psychological health. Participants gave their written consent and received monetary compensation for the completion of the study. This study was approved by the Medical Ethics Committee (CPP Sud-Est III, ID RCD: 2014-A011661-46).

2.2. Experimental design

Each trial started with a visual instruction indicating the type of trial (i.e., Indulge, Distance or Natural) for 3 s (seconds) (Fig. 1A), followed by the diffusion of one of the four categories of odors (apricot, pineapple, dark chocolate or milk chocolate) for 3.2 ± 0.8s, and synchronized with the respiration of the participants. Afterwards, a visual image corresponding to the odor was presented for 2 s (e.g. a visual picture of a pineapple pie following the smell of pineapple) (Fig. 1B). Finally, the participants had 5 s to select the price they were willing to pay for the presented food. Participants were able to choose one price from the five depicted on the screen (i.e. € 0.50, € 1.00, € 1.50 €2.00 or € 2.50); consistent with auction rules described by Becker-DeGroot-Marschack (BDM) (Becker et al., 1964; Plassmann et al., 2007). After the participant's response, a fixation cross was presented for 5.4 ± 0.6s.

Before the "Modulatory instruction and bidding task" began, participants received specific modulatory instructions for each trial type. For the Indulge condition, participants were asked to smell the odor and to keep looking at the presented food image while adopting thoughts that would increase their desire to eat the presented food immediately. For the Distance condition, participants were asked to smell the odor and keep looking at the presented food image while adopting thoughts that would decrease their desire to eat the presented food immediately. For the Natural condition, participants were asked to smell the odor and keep looking at the presented food image while allowing any thoughts and feelings that came naturally in that moment.

Before scanning, participants were asked to rate how hungry they felt on a continuous scale ranging from 0 = "not hungry at all", 50 = "moderately hungry", to 100 = "never been so hungry". They also rated the quantity of food they were able to eat, based on a similar continuous scale range from 0, "I cannot eat anything", to 100, "I could eat anything". This allowed us to evaluate the subjective hunger level of each participant. The fMRI task consisted of 120 trials divided into four sessions. Each session comprised 30 trials in a fixed order. Eight trials from each of the three conditions (resulting in 24 trials) and six "Air-clean" trials (for which there was no instruction, no odor, and no image presented), were presented in a random order. The four sessions were presented randomly to participants.

After scanning, blood samples were drawn by a nurse to measure peripheral ghrelin and leptin levels. This measure was provided by the Laboratoire de biologie medicale multi-site of the hospital of Lyon, which conducted an ELISA test with a commercial enzyme immunoassay (Human Leptin ELISA, Clinical range Cat.No.: RD191001100 manufactured by BioVendor for the leptin measure and Unacylated Ghrelin (human) Easy Sampling ELISA kit Cat No: A05319 and Acylated Ghrelin (human)

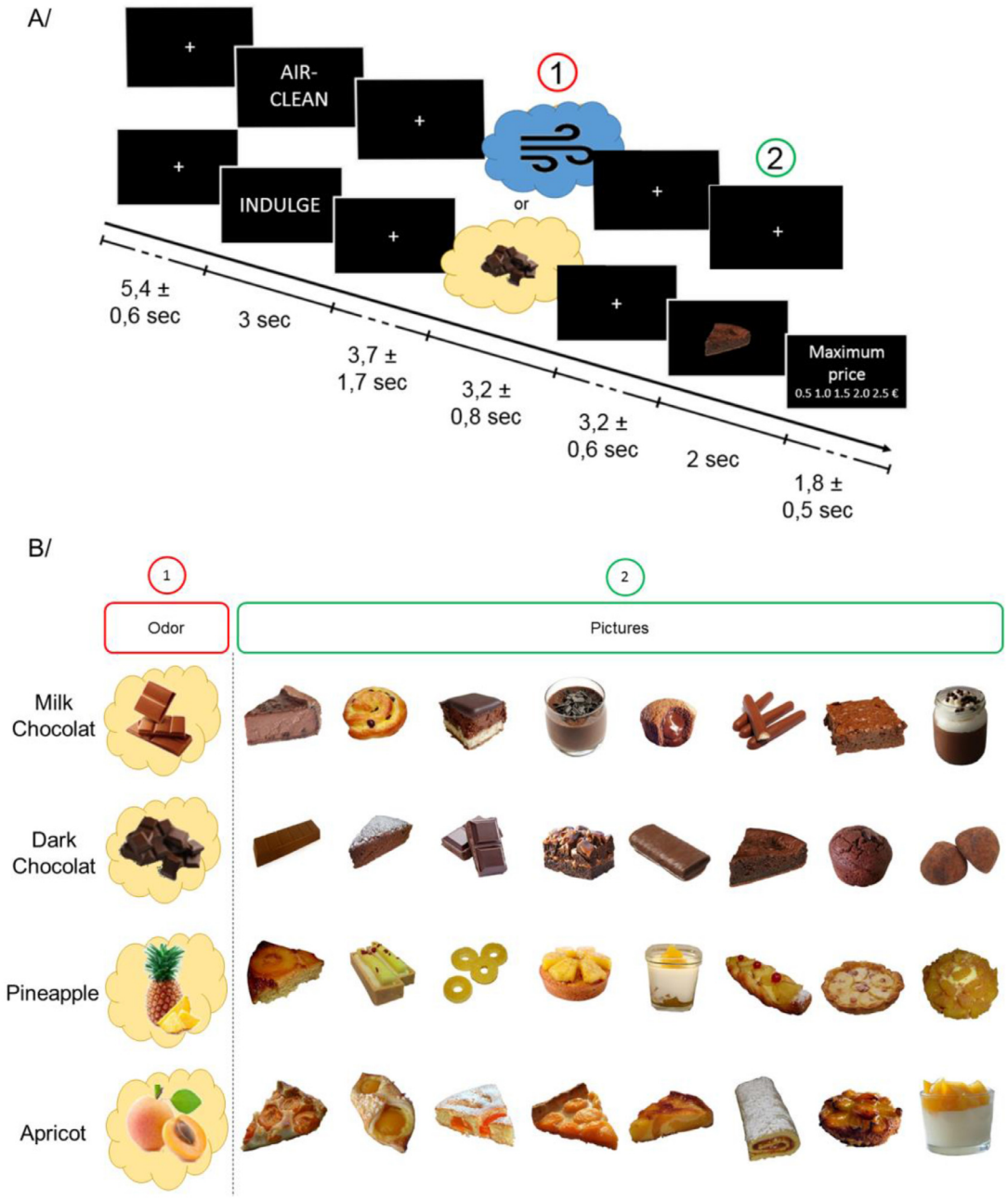

Fig. 1. *Experimental Design*. (A) Schematic overview of one trial of the task. The task was composed of four steps. First, hungry participants were given instructions (Indulge, Natural or Distance) to regulate their craving for food items. Second, they smelled one out of four odor categories (Apricot, Pineapple, Milk Chocolate or Dark Chocolate). Third, a picture of a food item associated to the odor was displayed (8 food pictures *per* odor category). Finally, participants were asked to rate how much they wanted to pay to get the food on a 5 points rating scale (from 0.5€ to 2.5€ with increment steps of 0.5€). (B) Overview of the food items presented. On each trial, a combination of one odor and one congruent picture (from the same food category) was presented.

Express ELISA kit Cat No: A05106 manufactured by Bertin Pharma for the total ghrelin level measure).

Finally subjects completed a post scan evaluation of their willingness to consume each of the foods depicted in the visual and olfactory stimuli 0-5, (rating 0 absolutely unwilling to consume, 5 absolutely willing to consume). The participants also rated the agreeability of the odors and their intensity. These data are found in supplementary Fig. S1.

2.3. Stimuli

Olfactory stimuli (apricot, pineapple, dark chocolate, milk chocolate, all EURACLI products, Chasse-sur-Rhone, France; Respective concentration vol/vol: 75%, 25%, 75%, 75%) and corresponding visual stimuli depicting desserts; 8 different images *per* odor type (Fig. 1B), were presented using a device adapted for fMRI olfactory/visual experiments and described in detail in Sezille et al. (Sezille et al., 2013). Airflow control, odor concentration and stimulus duration, as well as collection of participants' responses were all managed by the system, which was composed of a series of modules: 1/ an airflow source, 2/ a diffusion module controlling odorant duration and concentration through regulation of airflow, 3/ a mixing head used to *(i)* mix non-odorized air from the first module with a specific odorant (controlled by the second module) and (ii) send the diluted odor to the nose, 4/ a software enabling presentation of verbal material (in-

structions) and visual stimuli, 5/ a response box to record subjective ratings.

To ensure synchronization between fMRI measures and odor diffusion, olfactory stimuli were diffused at the beginning of each nasal inspiration. To this end, the respiratory signal was acquired using an airflow sensor that was integrated with an amplifier interface. A microbridge mass airflow (AWM2100V, Honeywell, MN, USA) allowed acquisition of both inhalation and exhalation phases. The airflow sensor was connected to a nasal cannula (Cardinal Health, OH, USA; 2.8 mm inner diameter tube) positioned in both nostrils. Sniffing was digitally recorded at 100 Hz and stored in the odor diffusion computer. Sniffs were preprocessed by removing baseline offsets, and aligned in time by setting the point when the sniff entered the inspiratory phase as time zero. Inhaled volume, max amplitude rate and sniff durations were calculated for the first sniff of every trial. Mean sniffing parameters during the entire odor presentation were also recorded.

The whole system was controlled using LabVIEW® software. A multiple function board (National Instruments, TX, USA) was used to acquire all experimental events (olfactory, visual, instructions), signals from the respiratory sensor and the response box, which allowed synchronization with the external system (the fMRI scanner).

2.4. MRI data acquisition

All MRI acquisitions were performed on a 3 Tesla scanner using EPI BOLD sequences and T1 sequences at high resolution. Scans were performed on a Siemens Magnetom Prisma scanner HealthCare, CERMEP Bron (single-shot EPI, TR / TE = 2500/21, flip angle 80 °, 45 axial slices interlaced 2 mm thickness 3 mm gap, field of view 230 × 230 × 132 mm). A total of 1120 volumes were collected over four sessions during the experiment, in an interleaved ascending manner. The first acquisition was done after stabilization of the signal. Whole-brain high-resolution T1-weighted structural scans (1 × 1 × 1 mm) were acquired for each subject, co-registered with their mean EPI images and averaged across subjects to permit anatomical localization of functional activations at the group level. Field map scans were acquired to obtain magnetization values that were used to correct for field inhomogeneity. Inhomogeneous distortion-related correction maps were created using the phase and magnitude of non-EPI gradient echo images. To do so, we used the FieldMap toolbox from SPM12 (Andersson et al., 2001; Hutton et al., 2002). We acquired two volumes with two different times of echo (one short = 4.92ms and one long = 7.38ms) resulting in two different phases. We followed the method implemented in SPM12 by calculating voxel displacement maps from the double phase and magnitude, based on the field mapping distortion correction approach outlined in (Jezzard and Balaban, 1995).

2.5. fMRI data preprocessing

Image analysis was performed using SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK, fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB R2013a (Mathworks, Inc.). Time-series images were registered in a 3D space to minimize any effect that could result from participant head-motion. Once DICOMs were imported, functional scans were realigned to the first volume, corrected for slice timing and unwarped to correct for geometric distortions. We used a non-linear procedure for unwraping with 6 degrees of freedom including translations and rotations. This was done using the FieldMap toolbox from SPM. It is accepted that the use of this method for distortion correction results improves co-registration between EPI and anatomical images. Finally, in order to perform group and individual comparisons, they were co-registered with structural maps and spatially normalized into the standard Montreal Neurological Institute (MNI) atlas space (152 spaces) using the DARTEL procedure implemented in SPM12 (Ashburner, 2007; Ashburner and Friston, 2009), resulting in a voxel size of 2 × 2 × 2 mm for the statistical analysis. Then images were spatially smoothed with an 8 mm isotropic full-width at half-maximum (FWHM) Gaussian kernel using standard procedures in SPM12.

2.6. fMRI data analysis and imaging statistics

To address the questions raised in the introduction, i.e. whether: (1 and 2) cognitive regulation modulates both sniffing and bidding behavior; 3) a common valuation system is involved in the valuation of odor/image stimuli or there are distinct brain regions (especially prefrontal regions: dmPFC vs dlPFC) supporting up- and down-regulation), we estimated three general linear models (GLMs). Each GLM was estimated in three steps. First, we estimated the model separately for each individual. Second, we calculated contrast statistics at the individual level. Third, we computed second-level statistics by carrying out various statistical tests on the single-subject contrast coefficients. All events defined with a boxcar function were convolved with the classical hemodynamic response function (HRF) and a high-pass filter was applied to remove low-frequency artifacts from the data (cut-off = 128 s).

Statistical analyses were performed using a conventional two-level random-effects approach with SPM12. All GLMs included the six motion parameters estimated from the realignment step and constant session at the end of the GLM. Statistical inference was performed at a standard threshold of $p < 0.05$, family-wise error (FWE) cluster-level corrected for multiple comparisons, with an initial cluster-forming threshold of $p < 0.001$ and a minimum number of $k = 40$ voxels otherwise noted. Note that it has been reported that the cluster level inference threshold could lead to an increase of false positive detection (Eklund et al., 2016). Nevertheless, using an initial cluster forming threshold of $p<0.001$ uncorrected is a reasonable statistical level inference for fMRI analyses and it has been shown to be sufficient to identify regions that are localized enough to be interpretable in many studies (Eklund et al., 2016; Woo et al., 2012).

2.6.1. Analysis of cognitive regulation during odor/image presentation

To determine the brain regions involved in cognitive regulation during the odor/image presentation, we used GLM1, consisting of 9 regressors of interest. Regressors R1–R3 modeled brain response related to the instructions according to the condition, respectively Natural (R1), Indulge (R2) and Distance (R3). R1-R3 were modeled as a boxcar function time-locked to the onset of the instruction with duration of 3 s. R4 to R6 denoted regressors during food stimuli delivery in Natural (R4), Indulge (R5) and Distance (R6) trials and were modeled as a boxcar function beginning at odor presentation and during the entire period of food odor/image presentation (mean 8.4 ± 1.6s). Finally, R7 to R9 modeled brain response related to the rating in the three regulatory instructions Natural (R7), Indulge (R8) and Distance (R9). R7-R9 were modeled as a boxcar function time-locked to the onset of the rating (willingness to pay) period with duration of response times (RTs: 1.8 ± 0.5s). Missed trials were modeled as a separate regressor over the duration of the entire trial. Finally, Air-clean trials were modeled separately using three distinct regressors. R10, denoting the instructions period from the Air-clean trials and modeled as a boxcar function time locked at the beginning of the instructions and during 3 seconds. R11, that denoted the stimulus period from the Air-clean trials, starting from the beginning of stimulus (even if the stimulus is a blank odor followed by a dark screen) and during 8 seconds. And R12, that denoted the rating period from the Air-clean trials and modeled as a stick function (because participants did not have to indicate their willingness to pay). The model also included motion parameters followed by session constants (representing our four runs and account for its effect) as regressors of no interest at the end of the GLM. To test for cognitive regulation a whole brain analysis was conducted and we computed the following contrasts: [Indulge (R5) > Natural (R4)] (Fig. 3; *Table 1*), [Distance (R6) > Natural (R4)] (Fig.. 4; Table 1) at the single level and then used a one-sample t-test at the group level on the single-subject contrast coefficients estimated.

Table 1
BOLD changes induced by cognitive regulation during processing of food items. **Clusters are reported at p < 0.05, family-wise error (FWE) cluster-level corrected for multiple comparisons (with an initial cluster-forming threshold of p < 0.001 and an extent k = 40 voxels).

Table 1. BOLD changes induced by cognitive regulation

	MNI peak cluster coordinates				
Effect of cognitive regulation during food perception	x	y	z	k	Z score
Indulge > Natural					
Right Superior Medial frontal cortex**	−4	58	21	1505	4.31
Left Superior Medial frontal cortex	−32	38	12	317	4.01
pre-SMA	8	16	54	271	3.78
Anterior Cingulate gyrus	0	32	−3	75	3.64
Left Superior Medial frontal cortex	−16	45	45	131	3.59
Indulge < Natural					
No brain region					
Distance > Natural					
Left Superior Lateral frontal cortex**	−24	52	22	6343	4.97
Dorsolateral Prefrontal cortex	44	16	46	561	4.27
Right Angular gyrus**	56	−54	27	722	4.22
Left Angular gyrus**	−46	−60	39	781	4.13
Right Superior Lateral frontal cortex**	20	46	30	1118	4.03
Distance < Natural					
No brain region					
**cluster reported at p<0.05 FWE whole brain cluster corrected (initial cluster-forming threshold of p<0.001, uncorrected and minimum extent k = 40)					

We also computed the opposite contrasts at the first level [Natural (R4) > Indulge (R5)] and [Natural (R4) > Distance (R6)] and then similarly used a one-sample t-test at the group level on the single-subject contrast coefficients.

2.6.2. Analysis of value computation in the natural context

We used GLM2 to investigate brain regions involved in the computation of value while experiencing food odor and image stimuli. We investigated the brain regions reflecting such value computation by searching for brain areas in which the BOLD response correlated with bids during the Natural trials. GLM2 had one regressor of interest R1, consisting of the food stimulus presentation and the entire rating period, parametrically modulted by the values of participants' bids in the Natural trials. The hemodynamic response of this categorical function was convolved with a boxcar beginning at the time of the first odor inhalation and terminating at the bid response (average duration of 10,2 ± 1.75s). The instruction period was regressed using a boxcar function, starting from the beginning of instructions with a duration of 3s. GLM2 also includes regressors denoting the stimuli in other conditions (i.e. Indulge and Distance). This regressor consisted of a boxcar function starting from the beginning of inhalation and lasting until the end of rating (average duration of 10.2 ± 1.78s). The model also included motion parameters and session constants (representing our four runs and account for its effect) as regressors of no interest at the end of the GLM. Finally, Air-clean and missed trials were modeled separately with a duration lasting for the entire trial. In order to reveal brain areas involved in the computation of value, contrasts on the bid parametric modulator on Natural trials were computed. Then, a one-sample t-test was performed at the group level on single-subject contrast coefficients (Fig. 5; Table 2).

We had strong *a priori* interest concerning the vmPFC and the ventral striatum because previous studies revealed that these regions perform value computations (Hare et al., 2009; Hutcherson et al., 2012; Kober and Mell, 2015; Metereau and Dreher, 2015). Region of Interest (ROI) analysis was thus conducted in a vmPFC ROI defined as an 8-mm radius sphere, centered at x,y,z = -2, 40, 2, based on a previous meta-analysis study showing that this region is involved in the processing of food value presented visually (Clithero and Rangel, 2013), leading to a vmPFC ROI of 257 voxels. Based on this same study, we also defined two ventral striatum ROIs (left VSTR, defined as a 8-mm radius sphere, centered at x,y,z = -8, 8, -6; right VSTR defined as a 8-mm radius sphere, centered at x,y,z = 10, 14, -4, both including 257 voxels. All ROI were defined using WFU_PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas). After ROIs creation, they were co-registered on the functional images in order to maintain voxel size.

Table 2
Brain areas correlating parametrically to the bid. ROI analyses were performed using a family wise error (FWE) peak cluster corrected for multiple comparisons. *small volume correction within a spherical ROI of 8 mm radius, centered on peak activity from previous literature (Clithero and Rangel, 2013; Metereau and Dreher, 2015).

	MNI peak cluster coordinates			
	x	y	z	Z score
Ventromedial PFC cortex *	6	42	3	3.42
Left Ventral Striatum *	6	18	−2	3.19
Right Ventral Striatum *	−6	14	−4	3.58
WTP x condition interaction	6	42	3	
No brain region	6	18	−2	

2.7. Behavioral analysis

Due to excessive head motion, one participant was removed from the fMRI analyses (resulting in n=24 for fMRI analysis). Another participant had to be excluded from the leptin/ghrelin Pearson correlation analysis because the hormonal assessment data from this participant was missing (resulting in n=23 for this analysis).

All statistical analyses were performed using SPSS v21.0 (SPSS Inc., Chicago, IL, USA). Normal distribution was assessed with a Shapiro-Wilk test. If data distribution was not normal, we performed a Friedman test, otherwise a repeated measure ANOVA was conducted. Then, we ensured that homoscedasticity of variances was respected using a Mauchly test. If not, we applied a Greenhouse-Geisser correction to our ANOVA. For multiple comparisons, *post-hoc* comparisons using the Bonferroni correction were conducted.

To sum up the behavioral statistics, we performed the following analyses. One-way repeated-measure ANOVA was conducted to test for any differences according to the conditions on the BID rating and reaction time. They included one factor with three levels (Indulge, Natural and Distance) (Fig. 2.A and 2.C respectively for BID and rating).

To control for the effect of food categories on the BID rating, a two-way repeated measure ANOVA was performed, including two factors.

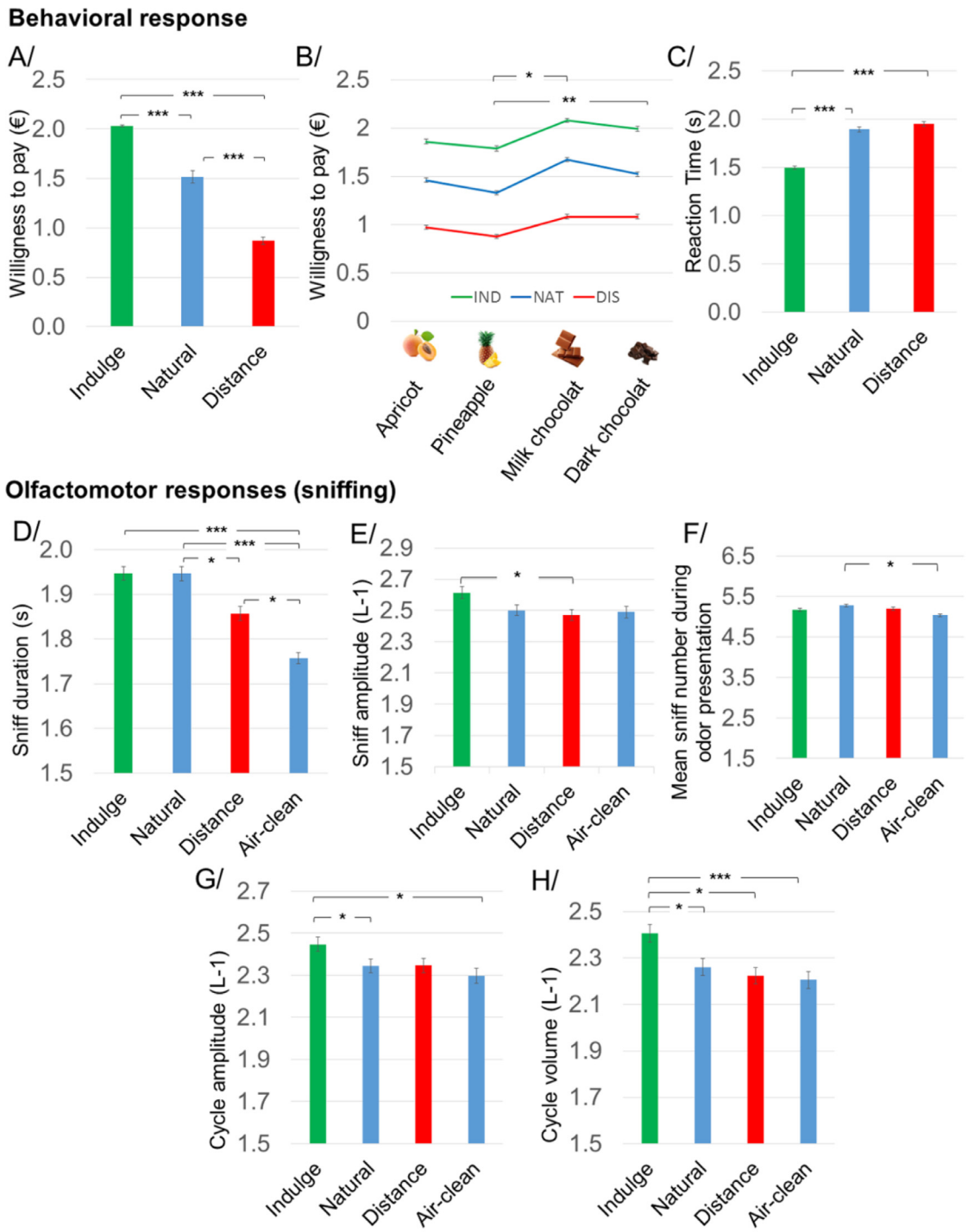

Fig. 2. *Behavioral and olfactomotor influence of cognitive regulation.* (A) Mean bid for each condition of cognitive regulation. Bids decreased in the Distance condition compared to Natural, while bids increased in the Indulge condition. (B) Mean bids across conditions and odor categories. Participants were less willing to pay for pineapple than for milk chocolate or dark chocolate. (C) Mean Reaction Times. A decrease in RTs was observed in the Indulge compared to the Natural and Distance conditions. (D) Mean duration of the first sniff. The duration of the first sniff was shorter in the Distance condition. (E) Mean amplitude of the first sniff. The average amplitude of the first sniff was greater in the Indulge condition compared to the Distance condition. (F) Mean number of sniffs during odor presentation. Higher number of sniffs occurred in the Natural compared to Air-Clean trials. (G) Mean amplitude of sniffs across the entire period of sniffing. Amplitude was greater in the Indulge condition compared to Natural and Air-Clean conditions. (H) Mean volume of sniffs across the entire period of sniffing. Volume was greater in the Indulge condition compared to Natural, Distance and Air-Clean conditions. Error bars show SEM. *** means $p<0.001$ ** means $p<0.01$ and * means $p<0.05$.

The first factor denoted the condition of regulation and included three levels (Indulge, Natural and Distance). The second factor denoted the food categories (Dark chocolate, Milk chocolate, Pineapple and Apricot) (Fig. 2.B).

Another two-way repeated measure ANOVA was performed, including a factor denoting the condition of regulation (Indulge, Natural and Distance) and a factor denoting gender (male and female).

Concerning the amplitude of the sniff (Fig. 2.E), the mean volume of the sniff cycle (Fig. 2.H), the mean amplitude of the sniff cycle (Fig. 2.G) and the total number of sniff cycles during the odor presentation (Fig. 2.F), a repeated measure ANOVA was performed including a factor denoting the condition of regulation (Indulge, Natural, Distance and Air-clean). Note that a Greenhouse-Geisser correction has been applied to the ANOVA performed for the total number of sniff cycles during the odor presentation.

Finally, because normality assumption for the duration of the first sniff was violated, we performed a Friedman test. We included one factor with 4 levels (Indulge, Natural, Distance and Air-clean) (Fig. 2.E)

3. Results

3.1. Behavior

Prior to scanning, participants rated their appetite on a continuous scale (ranging from "0"= not hungry at all, 50= moderately hungry; to "100"= never been so hungry). The food quantity participants would be willing to eat prior to scanning was also assessed on a similar continuous scale. Participants rated their appetite at 60.4% (SEM= 4.7) and their food quantity at 75.1% (SEM= 3.2). This procedure allowed us to ensure that participants felt subjectively hungry, and were willing to eat a large quantity of food. Furthermore, the post scan preference analysis revealed no statistical difference in the participants' willingness to consume the different foods, and no statistical difference in the agreeability of the different food odors. However, the pineapple food odor was perceived as more intense than the others and the visual cues for pineapple flavored foods were perceived as slightly, but significantly less attractive than those for other foods (Supplementary data Fig. S1). We also found a positive correlation between participants' appetite and their blood level of ghrelin (r=0.495, p=0.016) and a positive trend between blood level of ghrelin and the quantity of food participants were willing to eat (r=0.406, p =0.054).

We found that cognitive regulation had a significant effect on average bidding behavior ($F_{(2,46)} = 240.951$, p<0.001) (Fig. 2A). *Post hoc* analysis revealed that, compared to the Natural condition (the condition without cognitive regulation) (mean (M) 1.52€ ± (SEM) 0.011€), participants bid significantly more under the Indulge (the positive cognitive regulation condition) ((M) 2.03€ ± (SEM) 0.011€; paired $t_{(24)} = 12.508$ p<0.001) and less under the Distance condition (the negative cognitive regulation condition) ((M) 0.871€ ± (SEM) 0.007€; paired $t_{(24)} = 11.197$ p<0.001) (paired t-test with Bonferroni correction). We also controlled for possible interactions between regulatory conditions and food odor category (Apricot, Pineapple, Milk Chocolate or Dark Chocolate). This analysis revealed no significant interaction between cognitive regulation and types of food odor ($F_{(3,72)} = 0.934$, p=0.469). However, participants' bids differed according to the food category ($F_{(3,72)} = 118.079$, p<0.001) (Fig. 2B). Post-hoc tests revealed that participants bid less for Pineapple ((M) 1.33 ± (SEM) 0.026) compared to milk chocolate ((M) 1.61 ± (SEM) 0.027) (p < 0.005, paired $t_{(24)} = -3.145$) and compared to dark chocolate ((M) 1.49 ± (SEM) 0.027) (p < 0.05, paired $t_{(24)} = -2.789$).

Reaction Times (RTs) also differed between conditions ($F_{(2,46)} = 16.247$, p<0.001) (Fig. 2C). Participants' bids were faster in the Indulge condition ((M) 1.50s ± (SEM) 0.015s) compared to the Natural ((M) 1.90s ± (SEM) 0.024s; paired $t_{(24)} = 5.825$ p<0.001) and Distance conditions ((M) 1.95s ± (SEM) 0.025s) (paired $t_{(24)} = 5.221$ p<0.001).

3.2. Olfactomotor responses (sniffing)

A significant effect of condition was observed on the duration of the first sniff (Friedman test, $\chi^2_{(3)} = 24.75$, p < 0.001) (Fig. 2D, Duration of first sniff). Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level of p < 0.017. There was a significant decrease in the duration of sniffing in the Distance ((M) 1.86s ± (SEM) 0.015s) compared to the Natural condition ((M) 1.94s ± (SEM) 0.016s) (p =0.005, Z = -2.92). Participants inhaled for a shorter period during the Air-clean ((M) 1.76s ± (SEM) 0.012s) condition compared to the Distance (Z=-2.83, p=0.005), Indulge (Z=-3.73, p<0.001, (M) 1.95s ± (SEM) 0.016s) and Natural conditions (Z=-4.03, p<0.001). No significant difference in sniffing duration was found between the Indulge and Natural conditions (Z=-0.086, p = 0.932).

A significant effect of regulatory instructions was observed concerning the amplitude of the first sniff using an ANOVA ($F_{(3,72)}, = 4.248$, p = 0.008) (Fig. 2E, Amplitude of first sniff). A *post-hoc* test with the Bonferroni correction showed a significant decrease in the amplitude of sniffing in the Distance ((M) 2.47 L^{-1} ± (SEM) 0.035 L^{-1}) compared to the Indulge condition ((M) 2.61 L^{-1} ± (SEM) 0.033 L^{-1}) (p = 0.025, paired $t_{(24)} = -3.139$). No significant effect of condition was observed on the volume of the first sniff ($F_{(3,72)}, = 2.587$, p =0.06).

We next considered the entire sniffing period during odor presentation. We found a significant difference between conditions with respect to the total number of sniffing cycles ($F_{(3,72)}, = 3.962$, p = 0.011) (Fig. 2F, Mean sniff number). *Post-hoc* analysis revealed that participants had more sniffing cycles in the Natural condition compared to the Air-clean condition (p = 0.024, paired $t_{(24)} = -2.65$) but not between any of the Natural, Indulge or the Distance conditions.

A significant effect of conditions was observed on the average sniffing amplitude during the total sniffing period ($F_{(3,92)}, = 6.068$, p = 0.001) (Fig. 2G, cycle amplitude). A *post-hoc* test with Bonferroni correction showed a significant increase in the average amplitude of sniffing in the Indulge ((M) 2.45 L^{-1} ± (SEM) 0.035 L^{-1}) compared to the Natural conditions ((M) 2.34 L^{-1} ± (SEM) 0.035 L^{-1}) (p = 0.037, paired $t_{(24)} = -2.448$). The *Post-hoc* test also revealed a significant increase in the amplitude of sniffing in the Indulge compared to the Air-clean conditions ((M) 2.35 L^{-1} ± (SEM) 0.034 L^{-1}) (p = 0.011, paired $t_{(24)} = -2.346$). However, no significant difference in sniffing amplitude was observed between the Indulge and Distance conditions.

A significant effect of conditions was observed concerning the mean sniff volume during the complete sniffing period ($F_{(3,72)}, = 7.863$, p = 0.001) (Fig. 2H, Mean sniff volume). A *post-hoc* test with the Bonferroni correction showed a significant increase in the mean volume of sniffs in the Indulge ((M) 2.41 L^{-1} ± (SEM) 0.037 L^{-1}) compared to the Natural condition ((M) 2.26 L^{-1} ± (SEM) 0.036 L^{-1}) (p = 0.028, paired $t_{(24)} = -2.448$). They also revealed an increase in the average volume of sniffs in the Indulge compared to Distance conditions ((M) 2.22 L^{-1} ± (SEM) 0.036 L^{-1}). Finally, the *post-hoc* test also revealed a significant increase in the average volume of sniffing in the Indulge condition compared to the Air-clean trials ((M) 2.20 L^{-1} ± (SEM) 0.036 L^{-1}) (p = 0.004, paired $t_{(24)} = -2.346$). No significant effect of conditions was observed concerning the mean duration of sniffing during the entire period of odor presentation ($F_{(3,72)}, = 1.313$, p = 0.277).

We also investigated potential differences between men and women in their ability to regulate their appetite. Using a Two-way ANOVA, we found no significant difference between sex concerning bid ($F(_{5,120}) = 4.229$, p = 0.132) or RTs ($F(_{5,120}) = 5.603$ p = 0.099). When performing the same analysis on breathing parameters, we observed no significant differences for the volume ($F(_{7,168}) = 0.014$; p = 0.907), amplitude ($F(_{7,168}) = 1.31$; p = 0.282) and the duration of the first sniff ($F(_{7,168}) = 4.42$; p = 0.065). Despite the fact that men have a greater total lung capacity (LoMauro and Aliverti, 2018) we found no differences between men and women in breathing parameters. Finally, we did not

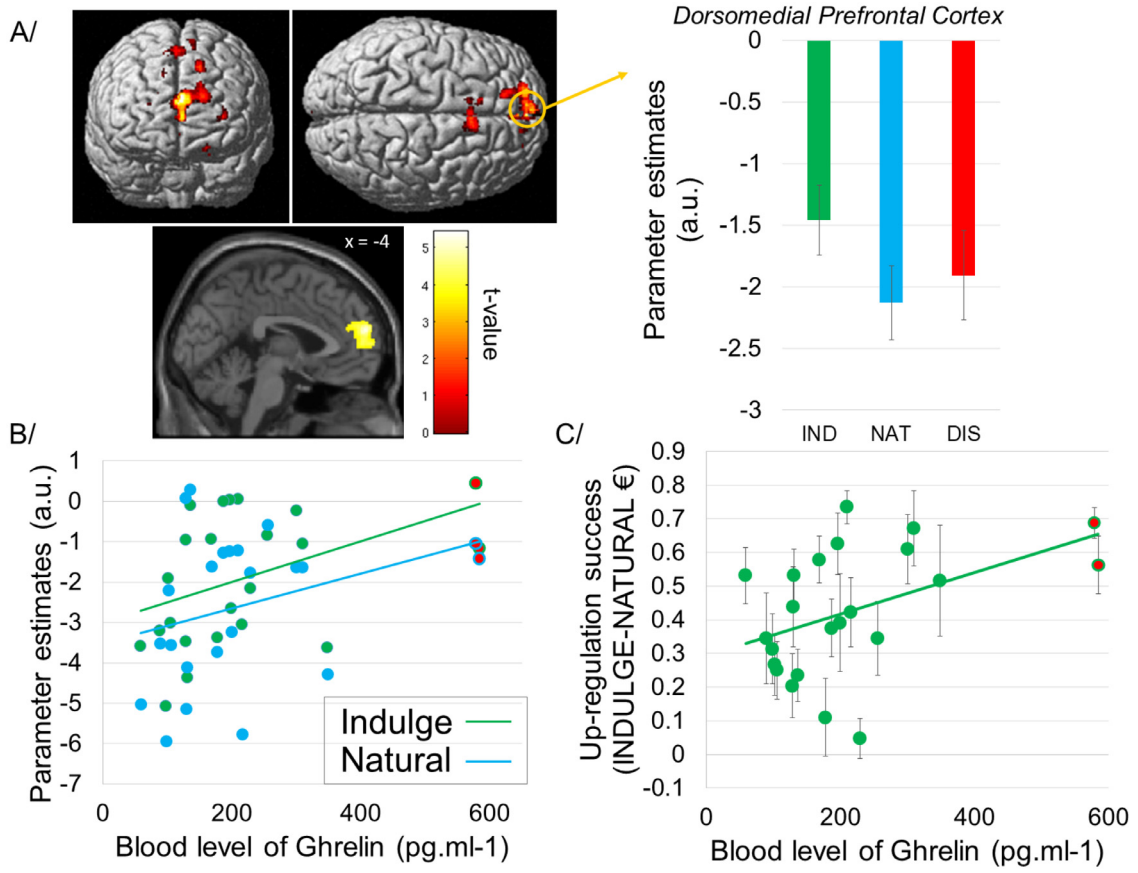

Fig. 3. *Up-regulation of appetite increases dmPFC activity and inter-individual differences linking up-regulation success and ghrelin levels*. (A) Up-regulation during the Indulge condition increased activity in the dorsomedial PFC (x,y,z: -4, 58, 21), at a whole brain FWE cluster-corrected threshold of p<0.05 (with an initial cluster forming-threshold of p<0.001 uncorrected and a cluster extend k of 40). Error bars show SEM. (B) Positive correlation between blood level of ghrelin and parameter estimates from the Indulge and Natural conditions. Correlation between beta in the Natural condition and ghrelin level r=0.469 (p=0.024) and between beta from the Indulge condition and ghrelin level r=0.511 (p=0.013). Correlation between the blood level of ghrelin and parameter estimates from the Indulge remains significant without the two outliers denoted with the red circle surrounded by green (one-tailed Pearson r = 0.405, p = 0.034). The correlation between the blood level of ghrelin and parameter estimates from the Natural condition did not survive after removing outliers (one-tailed Pearson p=0.052). (C) Positive correlation between up-regulation success and ghrelin level (r=0.373, p<0.05). Participants showing higher levels of ghrelin showed greater up regulatory success, as they were willing to pay even more during the Indulge condition. When outliers were removed from the analysis the correlation between the up-regulatory success and the blood level of ghrelin was no longer significant (one-tailed Pearson p = 0.072). Dots represent participants mean and SEM.

find any correlation between overall ghrelin levels or leptin levels and sniffing parameters.

3.3. fMRI results

3.3.1. Neurocomputational mechanisms of cognitive regulation of food

First, using GLM1, we searched for brain regions engaged in cognitive regulation during the odor/image presentation. As shown in Fig. 3, Table 1, when averaging over the period of odor/image presentation, BOLD response in the dorsomedial PFC was significantly higher in the Indulge compared to Natural condition (comparison Indulge > Natural) (x,y,z: -4, 58, 21; t = 5.43; p<0.05 Family-Wise Error (FWE) whole brain cluster corrected). To illustrate the response in this brain region, we extracted beta parameters in the three different conditions and plotted them (Bar Graphs). We also investigated the opposite contrast (Natural > Indulge). No brain region showed greater activity under Natural trials compared to Indulge trials.

Comparison of the Distance condition with the Natural condition (Distance > Natural) revealed a significant increase of the BOLD signal in the bilateral superior PFC (x,y,z: -24, 52, 22; 20, 46, 30; t = 6.76 and 4.94 for Left and Right respectively), the right dlPFC (x,y,z: 44, 16, 46; t = 5.35), the anterior cingulate cortex/supplementary motor area (ACC/SMA) (x,y,z: 3, 8, 62; t = 5.20) and bilateral angular gyrus (x,y,z: 56, -54, 27; -46, -60, 39; t = 4.22 and t = 4.13 for right and left respectively) (p<0.05 FWE whole brain cluster corrected) (Fig. 4, Table 1). Again, we also plotted the beta parameters from these regions in the three different conditions (Fig. 4). Finally, investigation of the contrast (Natural > Distance) revealed no brain region showing greater activity in Natural trials as compared to Distance trials. Note that we used cluster level inference with a p<0.05 FWE corrected threshold with an initial cluster-extent-forming threshold of p<0.001 uncorrected and an extend k of 40 voxels. It is a reasonable statistical level of inference for fMRI analysis and has been shown to be sufficient to identify regions that are localized well enough to be anatomically interpretable in many studies (Eklund et al., 2016; Woo et al., 2012).

3.3.2. Relationships between Ghrelin/leptin levels and brain activity in different regulatory conditions

Because up-regulation during the Indulge condition selectively increased activity in the dorsomedial dmPFC, we thought to investigate the link between this brain response and leptin/ghrelin levels. To determine the potential relationship between hormone levels and regulatory mechanisms, we conducted a correlation analysis between the beta extracted from the dmPFC ROI (8 mm radius sphere centered on the peak dmPFC cluster identified in the comparisons Indulge>Natural) and leptin or grehlin levels. We observed a positive correlation between

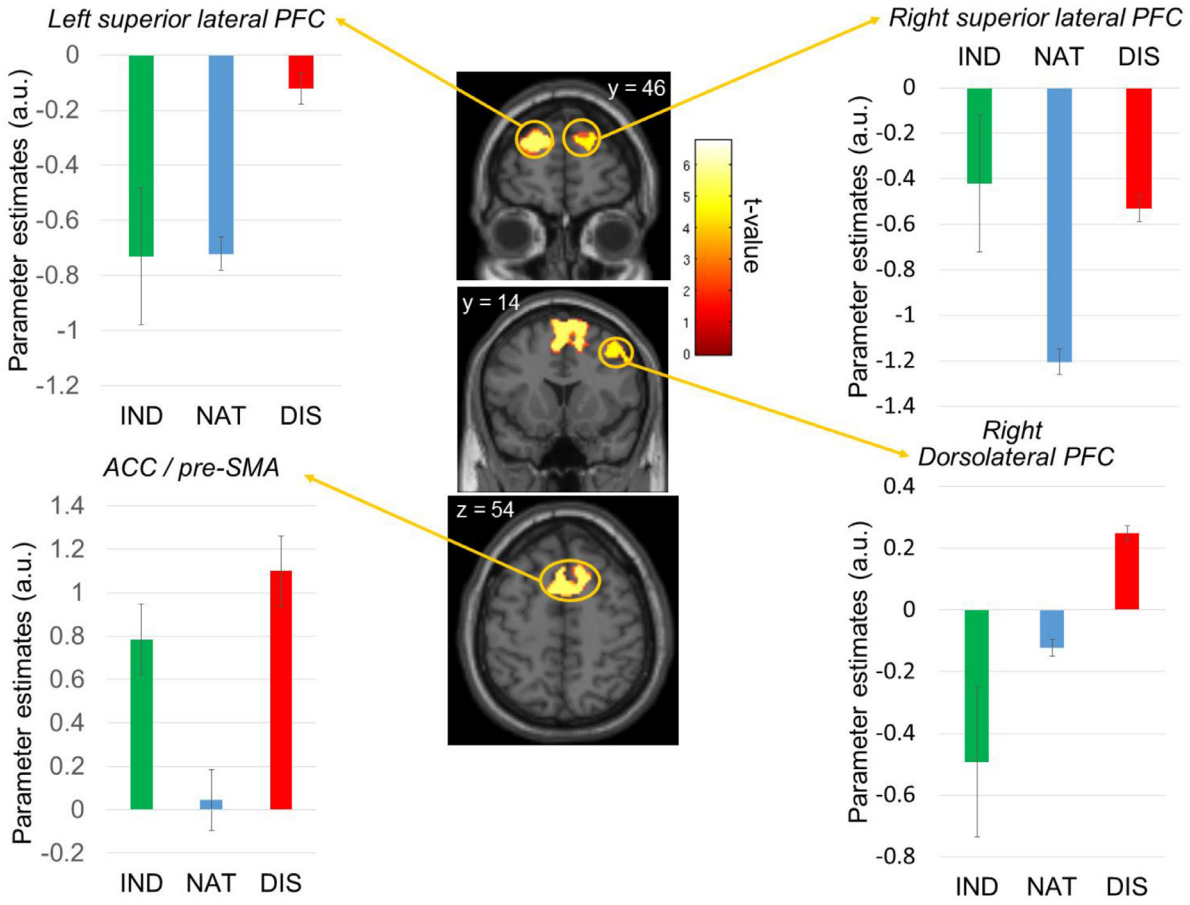

Fig. 4. *Down-regulation during the Distance condition increases activity of the bilateral superior PFC and the right dlPFC*. From top to bottom: Left superior lateral PFC (x,y,z: -24, 52, 22), the right dorsolateral PFC (x,y,z: 44, 16, 46) and right superior lateral PFC (x,y,z: 20, 46, 30); and ACC/pre-SMA (x,y,z: 3, 8, 62). Graphs indicate beta values extracted from clusters of activity. All analysis results were obtained using whole brain FWE cluster-corrected threshold of $p<0.05$ (with an initial cluster forming-threshold of $p<0.001$ uncorrected and a cluster extend k of 40). Error bars show SEM.

ghrelin level and betas extracted from the dmPFC ROI in the Indulge ($r = 0.469$, $p = 0.024$) and between ghrelin and betas in the Natural condition ($r = 0.511$, $p = 0.013$). No significant correlation was found between beta parameters from regions revealed by the contrast Distance > Natural and ghrelin level (Fig.. 3B). Note that in our group of subjects, two individuals were outliers for the blood levels of ghrelin (denoted as a red circle surrounded with their respective color, green for the Indulge condition and blue for the Natural condition). Even when these two participants were removed one-tailed Pearson test showed a significant positive correlation between ghrelin level and betas extracted from the dmPFC ROI in the Indulge ($r = 0.405$, $p = 0.034$) but not with the betas extracted from the dmPFC ROI in the Natural condition ($p = 0.052$). The same procedure was conducted for leptin level but no significant correlations were revealed.

Finally, we defined the 'regulatory success' as the positive WTP difference between the Indulge and Natural conditions for a given food (represented by an odor followed by a picture) (i.e. when participants bid more in the Indulge condition than in the Natural condition). The same procedure was used to compute the absolute value of the difference in WTP between Distance and Natural conditions for the cases where participants bid less in the Distance than in the Natural condition. We then conducted Pearson correlation analysis to determine if the ghrelin level is correlated with regulatory success when up- or down regulating. We observed a significant correlation between ghrelin levels and up-regulation ($r= 0.373$; $p = 0.002$) but not between ghrelin levels and down-regulation ($p = 0.516$) (Fig. 3C). Here again the correlation is driven by two outliers for the blood level of ghrelin. On removal of these two outliers, the one-tailed Pearson correlation revealed no significant positive correlation ($p = 0.072$). Additionally, no correlations between leptin level and up-regulation success or downregulation success were revealed (Pearson correlation test, respectively $p = 0.641$ and $p = 0.972$).

3.3.3. *Subjective value computation at the time of Willingness to Pay*

Next, we searched for brain areas engaged in odor/image value computation using GLM2. We found that the vmPFC (x,y,z: 6, 42, 3; $t = 3.96$), and bilateral VSTR (x,y,z: -6, 14, -4; $t = 4.20$ and 6, 18, -2; $t = 3.62$ respectively left and right) positively correlated with participants' bid in the Natural condition ($p<0.05$, FWE corrected within small volume correction) (Fig.. 5, Table 2). Note that we used Natural trials only to determine brain areas correlating with WTP because there was not enough variation in the bids in the Indulge and Distance conditions to perform regression analyses between WTP and the BOLD signal. Indeed, WTP were almost always high in the Indulge condition and almost always low in the Distance condition, relative to the Natural condition. This prevented us from observing value signals across all conditions and testing for changes in slopes between value representation (as indexed by brain regressions with WTP) and regulatory conditions. Thus, to investigate whether regulatory instructions modulated activity in the vmPFC and bilateral striatum, we defined spherical ROIs over the vmPFC and bilateral VSTR based on previous analyses reporting these regions as key areas for valuation (Clithero and Rangel, 2013; Hutcherson et al., 2012; Kober and Mell, 2015; Metereau and Dreher, 2015; Hare et al., 2009). Within these

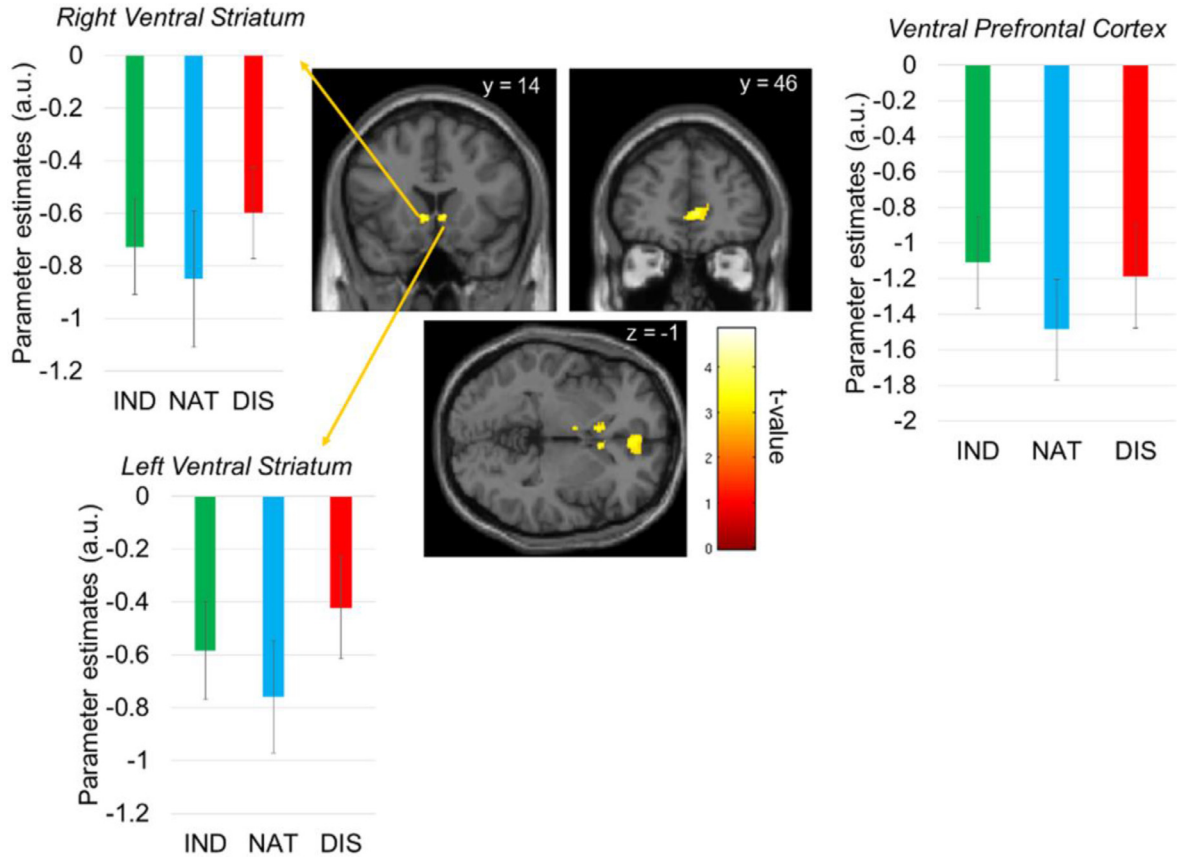

Fig. 5. *vmPFC and bilateral striatum correlate with bids in the Natural condition.* Activity in the vmPFC (x,y,z: 6, 42, 3) and bilateral striatum (x,y,z: -6, 14, -4 and 6, 18, -2 respectively for right and left striatum) correlate with the willingness to pay during the Natural condition with no differential effect of the regulation strategies on these regressions. All activations are reported at a whole brain FWE peak corrected threshold of $p<0.05$. Here the activation map is presented at $p<0.001$ uncorrected for display. Beta extracted within these regions came from GLM 2. Error bars show SEM.

ROIs, we used GLM1 to search for significant differences between regulatory instructions. The results revealed no significant differences across conditions within these ROIs. To illustrate this, we extracted beta parameters from these ROIs in the three different conditions and plotted them (Fig. 5).

4. Discussion

One important aspect of this study was to investigate, in food deprived participants, the neural mechanisms engaged in cognitive regulation of food stimuli presented in the visual and olfactory domains. Both willingness to pay for food and sniffing parameters were modulated by regulatory conditions, indicating reliable regulatory mechanisms at the behavioral and olfactomotor levels. In particular, evidence from analysis of sniffing duration showed that cognitive regulation in the distance condition acts spontaneously to limit sensory exposure to odor stimuli to regulate appetite. There is a possibility that a subconscious desire to fulfill the experimenters' expectations might have influenced the behavior of the participants. However, the participants' willingness to pay accurately reflected their personal food preferences expressed in the post-scan questionnaire. Furthermore, the spontaneous regulation of olfactomotor behavior, to reduce or increase the participants' exposure to tempting olfactory stimuli in the Distance and Indulge conditions respectively is in agreement with a genuine attempt to engage in cognitive regulation of appetite.

At the brain system level, increased dorsomedial PFC activity occurred during up-regulation of appetite (Fig. 3A), whereas a brain network, including the bilateral superior PFC, the right dlPFC and the ACC was more engaged during down-regulation of appetite as compared to the Natural condition (Fig. 4). Activity in the valuation system, including the vmPFC and bilateral striatum correlated with increasing WTP for food, but was not modulated by appetite regulatory instructions, confirming that engagement of this brain system is relatively automatic (Fig. 5). Together, these results demonstrate the existence of separate brain systems responding or not to appetite regulation when subjects are hungry.

Our findings provide novel insights to the neurobiological mechanisms involved in the cognitive regulation of bimodal food cues. In fact, food stimuli presented in both olfactory and visual domain represent a richer and more realistic stimuli than visual stimuli alone. First, cognitive regulation modulated the duration (Fig. 2D) and the amplitude (Fig. 2E) of the first inspiration, showing that parameters of the olfactomotor system are under modulation by cognitive regulation. Our results extend early findings on cognitive regulatory mechanisms, and highlight the fact that human sniffing is influenced by internal states, such as motivation or homeostatic state. For example, hunger increases sniff duration compared to satiety, even when sniffing clean air (Prescott et al., 2010). Cognitive regulation also modulated olfactory parameters over the entire sniffing period (Figs. 2H, 2G). Together, these olfactomotor results suggest that subjects have meta-cognition regarding the impact of odors on their self-control, and therefore try to modulate their sniffing parameters. The decrease of the sniffing parameters observed in the Distance condition reduces temptation caused by the smell of food and thus regulates the willingness to consume this particular food item. The inverse pattern observed in the Indulge condition matches with the inverse strategy. This is an important finding because much remains to be learnt about the channels through which individuals exercise dietary control. Finally, participants' WTP for food was higher in the Indulge condition,

as compared to the Natural condition, whereas they bid less under the Distance condition (Fig. 2A). These findings extend previous results restricted to the visual modality to bimodal food stimuli (Boswell et al., 2018; Hutcherson et al., 2012) and further show that humans are able to regulate their WTP when the food is presented in both olfactory and visual modalities.

The increased engagement of the dorsomedial PFC (dmPFC) observed with up-regulation of appetite towards food stimuli is consistent with the fact that this brain region shows a specific heightened response to food when subjects are hungry (Anderson et al., 2006; Giannopoulou et al., 2018; LaBar et al., 2001) (Fig. 3A). This finding supports the idea that this brain region modulates motivation towards food. This was not simply a reflection of brain activity changes being caused by altered olfactomotor behavior because despite inclusion of mean volume of the sniff cycle as co-variate in the first level of analysis the same brain regions were identified as significantly activated in the Indulge compared to the Natural condition (Fig. S3). Similarly, inclusion of the mean amplitude of the sniff cycle resulted in similar brain activities (Fig. S5). Finally, inclusion of volume of first sniff as a co-variate in the first level of analysis resulted in identification of activation in the same brain areas, although statistical thresholds did not survive family-wise error corrections. This is probably explained by the failure to obtain first sniff parameters for some trials, which reduced the statistical power of comparisons. These results suggest that during up-regulation, activity within the dmPFC increases together with a concurrent increase in appetite towards food stimuli. In obese populations, a meta-analysis revealed higher activity of the dmPFC when viewing food pictures (Brooks et al., 2013).

Conversely, the dlPFC, bilateral superior PFC and the ACC were more active when participants down-regulated their appetite towards bimodal food stimuli (Fig. 4). Again, this was not a reflection of the brain activity change caused by altered olfactomotor behavior. The same brain regions were identified as significantly activated in the Distance compared to Natural condition when including the mean volume of the sniff cycle as co-variates in the first level of analysis (Fig. S4) or the mean amplitude of the sniff cycle (Fig. S6). The dlPFC is known to be engaged in regulation of appetite for visually presented food stimuli (Hutcherson et al., 2012a; Kober et al., 2010; Giuliani et al., 2014; Tusche and Hutcherson, 2018) and the ACC plays a critical role in response inhibition and in the selection of appropriate behavior to resolve situations such as action suppression (Cole and Schneider, 2007; Simmonds et al., 2008). Moreover, the bilateral superior PFC has been associated with cognitive strategies to suppress the desire for food stimuli (Siep et al., 2012). Engagement of a brain network including the dlPFC has been reported in down regulation of emotional responses to odors (Billot et al., 2017). Furthermore, regulation-related neural activation patterns in the right dlPFC area have been shown to reliably predict how well participants reduce the importance of taste in food choices (Tusche et al., 2018). Increased dlPFC response has been observed during down-regulation of negative emotions, and decreased dlPFC activity occurred during down-regulation of positive emotions (Ochsner and Gross, 2005). Together, these findings are consistent with the hypothesis that cognitive regulation of appetite and emotional regulation may share common neural substrates.

When investigating the brain systems engaged in the valuation of food items in response to bimodal realistic cues in the absence of cognitive regulation, (Natural condition), we observed engagement of the valuation brain system, consisting of the vmPFC and the bilateral striatum (Fig. 5). These brain regions have previously been shown to be key for valuation of food items presented visually (Clithero and Rangel, 2013). We extend these previous results to multimodal situations in which food is experienced in both the visual and olfactory modalities. Such vmPFC engagement in the valuation of food items is much closer to experiencing real food (combining vision, smell and taste). This brain region has also been observed during anticipation of salient food (liquid) reinforcers that are delivered inside the scanner (Metereau and Dreher, 2015; O'Doherty et al., 2002). Thus, vision and smell play a key role in constructing a unified and co-occurring percept defined as flavor when anticipating and experiencing food items.

It should be noted that none of the brain valuation regions were modulated by cognitive regulation. In fact, distinct brain regions were engaged during the Indulge and Distance conditions. This confirms that valuation is relatively automatic, as previously suggested (Lebreton et al., 2009) and that cognitive regulation of food odor and image does not modulate the valuation system itself. A number of previous studies using similar paradigms but only with food presented in the visual domain (Hare et al., 2009, 2011; Hutcherson et al., 2012; Krishna, 2012), have reported that regulation involves the modulation of value signals in the vmPFC, as well as interaction with regions like the dlPFC. However, a number of studies failed to observe such changes in modulation of the vmPFC during cognitive regulation of decision making, suggesting an alternative hypothesis (Hollmann et al., 2012; Yokum and Stice, 2013; Tusche et al., 2018). It is possible that in our study, as in these latter studies, cognitive regulation alters value representations at a relatively low level, by amplifying or diminishing attribute representations directly in a distributed set of specific, dedicated attribute-coding areas. Consistent with this possibility, a recent study observed that cognitive regulation did not operate at higher levels in centralized, domain-general value integration areas such as the vmPFC (Tusche and Hutcherson, 2018). Instead, cognitive regulation of decision-making altered value representations at a relatively low level, representing food attributes in a dlPFC region.

Finally, correlational analysis revealed a positive relationship between blood levels of ghrelin and BOLD response in the dmPFC that up-regulated the subjective value of food items in the Indulge condition (Fig. 3B). This correlation remains significant even if we excluded the two outliers from the analysis. In addition, individuals with higher blood levels of ghrelin tended to be better at exercising up-regulation as they showed increased regulatory success when comparing bids from the Indulge vs Natural conditions (Fig. 3C). Thus, the relationship between dmPFC activity and ghrelin levels may be a neurobiological marker for up-regulation success. Ghrelin regulates food intake (Date et al., 2001; Müller et al., 2015) and levels of ghrelin positively correlate with increased hunger and with increasing activity in large brain networks involved in the regulation of feeding and in the appetitive response to food cues (Batterham et al., 2007; Goldstone et al., 2004; Jones et al., 2012; Wei et al., 2015; Zanchi et al., 2017). All these studies showed increased neural response to food pictures in regions of the brain engaged in encoding the automatic incentive value of food cues, but did not investigate how ghrelin modulates brain regions engaged with up-regulation of food cues, as in the current study. Ghrelin may act on the brain through several mechanisms, including ghrelin receptors in the gut relaying information *via* the vagus nerve (Date, 2013), the hypothalamus regulating feeding behavior, and the dopaminergic system (Abizaid et al., 2006; Perello et al, 2012). Our results suggest that the dmPFC plays a crucial role in the relationship between ghrelin and up-regulation of feeding behavior. Note that we did not observe any relation between ghrelin level and sniffing parameters. Nevertheless, we revealed a correlation between up-regulation success and ghrelin levels and between dmPFC activity and ghrelin level, suggesting that ghrelin facilitates both upregulation success and its neural substrates. This result should be carefully interpreted as two outliers were driving the significance of the correlation, although, their values were well within the normal range for healthy subjects (Cummings et al., 2004). In addition, no significant results were found for the leptin and down-regulation success or brain activity related to the down regulation condition. We conclude that leptin is not a modulator for down-regulation of food presented in a visual and olfactory domain in hungry participants. In addition, leptin is not the only hormone modulating energy balance and it is not excluded that other hormones such as GLP-1 or PYY, which are known to promote satiety (Karra et al., 2009; Neary et al., 2005; Shah and Vella, 2011), could participate to the opposite phenomenon

in the down regulation condition. Further pharmacological studies are required to confirm the results indicating the presence of a link between blood level of ghrelin and brain activity and behavioral modulation related to the up-regulation condition.

One limitation of the study is that ghrelin/leptin correlations were performed on a sample size of twenty-four subjects. Further studies would benefit from being tested in a larger group in the future.

5. Conclusion

Together, our results demonstrate that in the context of hunger, up- and down-regulation of appetite towards realistic food stimuli presented in the olfactory and visual domains are each mediated by distinct brain networks. The medial prefrontal cortex is engaged in up-regulation whereas the lateral prefrontal cortex is engaged in down-regulation. Our findings also provide new insights to the relationship between higher-level brain regions engaged in up-regulating food consumption and ghrelin.

Data and code are available

All statistical T-map are available following this link: https://neurovault.org/collections/7767/.

Original data and codes are available upon request to Jean-Claude Dreher at dreher@isc.cnrs.fr.

Declaration of Competing Interest

The other authors declare no conflict or no competing of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.117811.

Credit authorship contribution statement

R. Janet: Methodology, Writing - original draft, Writing - review & editing. **A. Fournel:** Investigation. **M. Fouillen:** Methodology, Investigation. **E Derrington:** Writing - review & editing. **B. Corgnet:** Writing - review & editing. **M Bensafi:** Conceptualization, Investigation, Resources, Writing - original draft. **JC. Dreher:** Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Funding acquisition, Supervision.

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