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Effects of hunger state on the brain responses to food cues across the life span

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A B S T R A C T

The abundant exposure to food cues in our environment is one of the main drivers of overconsumption. Food evaluation is important for the regulation of food intake by the brain and it's interaction with hunger state. Children are especially susceptible to food cues. Understanding the mechanisms behind this regulation in healthy individuals across the life span can help to elucidate the mechanisms underlying overconsumption and aid the development of future obesity prevention strategies. Few functional neuroimaging studies have been done in children and elderly. Furthermore, it is unknown how hunger state affects neural food cue reactivity in these groups, since this has not been examined consistently.

We examined the effects of hunger state and age on the brain responses to low- and high calorie foods. On two mornings, 122 participants (17 children; 38 teens; 36 adults; 31 elderly) performed a food image viewing task while being scanned using fMRI, either fasted or sated.

Hunger induced greater activation during high versus low calorie food image viewing than satiety in the bilateral dorsomedial (dmPFC) and in the right dorsolateral prefrontal cortex (dlPFC) across all age groups. There was no significant main effect of age group on high versus low calorie food image viewing and no interaction between age group and hunger state.

The greater activation of the dlPFC across all age groups during high calorie food image viewing in a fasted state might reflect increased inhibitory control in response to these foods. This may underlie the ability to resist overconsumption of high calorie foods. Furthermore, increased medial prefrontal cortex activation during hunger might reflect increased reward value of high calorie foods, which declines with satiation. Further studies are needed to better understand these results. Notably, overweight and obese individuals should be included to examine whether these responses are altered by weight status across the life span.

Introduction

During the day we are continuously exposed to food cues. Food cue exposure can influence the motivation to eat (Ferriday and Brunstrom, 2011). When we perceive a food cue, multiple processes are triggered in our brain such as preparation for ingestion and food evaluation. Examining the brain responses to food cue exposure may help to elucidate the mechanisms underlying unhealthy eating behavior such as overconsumption. Moreover, brain reactivity to food cues has been shown to predict food choice (Mehta et al., 2012; van der Laan et al., 2012), snack consumption (Lawrence et al., 2012), future weight gain in adolescent girls (Yokum et al., 2011), and women (Demos et al., 2012), weight status in women (Killgore et al., 2013) and outcome in a weight-loss program (Murdaugh et al., 2012). However, relatively little is known about the impact of developmental changes on the brain responses to food (van Meer et al., 2016a). Furthermore, hunger state (in interaction with calorie content) is known to affect food reward processes in the brain (Siep et al., 2009) and the effect of hunger state may change with age.

When normal weight adults look at food images compared with non-food images, areas in the appetitive brain network become active. This network centers around four interconnected brain regions: the amygdala and hippocampus, the orbitofrontal cortex (OFC), the striatum, and the insula (Dagher, 2012; Van der Laan et al., 2011). Furthermore, areas involved in attention and visual processing (such as the lateral occipital complex) have been reported to consistently become more active in response to food compared with non-food image viewing (Van der Laan

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et al., 2011). Several studies have examined the brain responses to high versus low calorie food images (e.g., Killgore et al. (2003); Rothemund et al. (2007); Goldstone et al. (2009)) or similar comparisons like fattening and non-fattening food images (Mehta et al., 2012). In a meta-analysis, there was low concurrence among such studies, with the most consistent area stretching from the hypothalamus to the right ventral striatum (Van der Laan et al., 2011). However, the number of studies included was quite low and there were several differences between the studies which likely decreased the comparability.

Brain responses to food likely change with increasing age because of structural and functional brain alterations. The brain does not reach full maturity until 21 years of age. Crucially, not all brain areas mature at the same rate. For example, relatively greater changes have been reported in the prefrontal cortex (PFC) compared with other brain regions between the ages of 8 and the early 20-s for gray matter reduction (Sowell et al., 1999), synaptogenesis (Huttenlocher and Dabholkar, 1997), myelination increases (Giedd et al., 1999) and resting level metabolism (Booth et al., 2003). Furthermore, as people grow old, there are gradual structural changes such as decreases in gray matter density, synaptic pruning and cell shrinkage (Sowell et al., 2003).

Casey et al. (2008) argue that there is a combination of heightened responsiveness to incentives and relatively immature impulse control in adolescence, leading to increased impulsiveness and reward-seeking behavior. In line with this, activation in reward-related areas during monetary reward anticipation has been shown to increase with age from childhood (10 y) to early adulthood (25 y, Hoogendam et al. (2013)). This activation decreases from adulthood (age 40) into senescence (age 70, Vink et al. (2015)). Since there is wide overlap in the brain circuits for monetary and food reward processing (Sescousse et al., 2013), a similar age-related pattern might be expected in response to palatable food exposure.

A recent meta-analysis showed that children most consistently activate areas of the appetitive brain network in response to visual food cues, similar to adults (van Meer et al., 2015). Also, there were some indications that children may not activate areas in the ventrolateral prefrontal cortex (vlPFC; involved in cognitive control) whereas adults do. However, there were not enough studies in children to properly confirm this finding (van Meer et al., 2015). A recent study comparing children (10-12y) and adults found higher activation in the precentral gyrus (involved in motivation) in children in response to viewing unhealthy compared with healthy food images (van Meer et al., 2016b). Several studies in adolescents examined the brain responses to high and low calorie food cues using paradigms other than food image viewing and found greater response to high calorie foods in the OFC (Feldstein Ewing et al., 2017) and anterior cingulate cortex (ACC; Yokum et al. (2011)). However, in these studies adolescents were not compared to other age groups, and the effect of hunger state was not examined. In older adults and elderly very little is known about possible changes in visual food cue reactivity (van Meer et al., 2016a). One study showed that, in adults aged between 20 and 53, increasing age was associated with a lower response in the dorsolateral prefrontal cortex (dlPFC) in response to food images (Cheah et al., 2014). There is a growing literature though on changes in taste-related activation of gustatory and reward processing areas in young, middle-aged and elderly adults (Green et al., 2013; Hoogeveen et al., 2015; Jacobson et al., 2010; Rolls et al., 2015).

Hunger has a direct effect on the salience of food cues. Activation in the hippocampal gyrus and amygdala has been found to increase during hunger across several studies. Similarly, lateral OFC (vlPFC) activation in response to food images was found to increase in a hungry compared to a sated state (Van der Laan et al., 2011). Fasting often increases responses to high-calorie foods in areas associated with processing of reward and stimulus salience (OFC and striatum) and the processing of visual cues (fusiform gyrus) (Pursey et al., 2014). Satiation compared with a normal between-meal hunger state was associated with an increase in dlPFC activation and a decrease in OFC and medial OFC activation in response to the sight and taste of foods in lean young adults (Thomas et al., 2015).

In adults aged between 20 and 53 y, increasing age was associated with a smaller difference in neural food cue reactivity between fasted and fed states in areas involved in reward such as the striatum and in the dlPFC (Cheah et al., 2014). However, no studies have examined the effect of hunger on food cue reactivity in elderly. Thus, studies directly comparing brain responses to food cue exposure between age groups and hunger states are lacking.

Therefore, the primary objective of this study was to compare brain responses to food cues across the life span and to examine to what extent these are modulated by hunger state. Since hunger state may interact with the caloric content of the foods, we included both low and high calorie food images. We expected lower activation in frontal areas such as the dlPFC in children, teens and elderly compared to adults, especially when sated. In addition, we hypothesized that there would be smaller differences between hungry and sated states in children, teens and elderly compared to adults in reward related areas such as the OFC and striatum. In addition, we hypothesized increased activation in teens compared to children in reward-related regions like the striatum and OFC for the response to high-versus low-calorie foods and a decline in such activation with aging.

Materials and methods

Participants

We included healthy children, teens, adults and elderly with a normal weight (i.e., BMI 20–25 kg/m^2 equivalent) in four age groups (between 8 and 10, 13–17, 25–45 and 65–75 years of age). Participants were recruited in three countries (The Netherlands, Scotland and Greece). These age groups were chosen to ensure that the vast majority of the children were pre-pubertal, teens pubertal, adults post-pubertal and most likely pre-menopausal and elderly post-menopausal. Additionally, the gap between the age groups maximized the chance of finding differences between the groups. Additional criteria: right-handed, non-smoking, with a stable weight (did not gain or lose >5 kg of body mass in the past 6 months), no use of medication (except aspirin/paracetamol and oral contraceptives and anticoagulants and cholesterol medication in elderly) and no current alcohol consumption of >28 units per week. Furthermore, common fMRI exclusion criteria (e.g. claustrophobia, pregnancy and metal implants in the body) and criteria that might influence response to food cues (e.g. claustrophobia, food allergies, special diets, eating disorders, gastrointestinal disorders or metabolic or endocrine disease, highly restrained eating scores on the Dutch Eating Behavior Questionnaire (Van Strien et al., 1986) or its child version (van Strien and Oosterveld, 2008) were used. In addition, runs with excessive movement were excluded from the analyses. 145 eligible participants enrolled in the study, 10 participants (4 adults, 3 elderly, 2 children, 1 teen) were excluded because they did not have a successful viewing task run for each condition, 8 participants (6 children and 2 teens) were excluded due to excessive movement (see section 2.4.2), one child had a neurological disorder, the remaining two children from Scotland were excluded because adding an extra variable to the already low number of children was not preferable, one adult was excluded because he fell asleep and one additional child was excluded due to average signal during food versus non-food image viewing was >2 SD different from the group mean and since its movement was on the upper boundaries of our threshold it was excluded from the analysis. The resulting sample included in the analyses consisted of $n = 122$ participants (17 children, 38 teens, 36 adults, 31 elderly) (see Table 1 for details).

Experimental design

Study procedures

The study consisted of two morning MRI scan sessions. On both days, the participants came in after an overnight fast of at least 10 h. During the sated condition session participants were scanned after the

Table 1
Participant characteristics.

	Children n = 17	Teens n = 38	Adults n = 36	Elderly n = 31
Country ratio (NL:SCT:GR)[2]	17:0:0	26:5:7	19:8:9	22:6:3
Gender (Male:Female)	6:11	21:17	18:18	14:17
Age (y)[1]	9.6 ± 0.9	15.5 ± 1.7	32.6 ± 5.8	69.8 ± 3.2
(SDS) BMI (kg/m^2)[1, 3]	−0.33 ± 0.8[a]	0.34 ± 0.8[a]	23.0 ± 1.8[b]	21.3 ± 7.4[b]
Interscan interval (days)[1]	9.6 ± 2.9	9.7 ± 6.1	8.5 ± 4.2	9.3 ± 4.1
First visit (Sated:Hungry)	8:8	19:19	14:22	13:18
Amount liquid breakfast consumed (mL)[1]	277 ± 108	445 ± 51	510 ± 80	492 ± 124

[1]Mean ± SD. [2]NL: Netherlands, SCT: Scotland, GR: Greece. [3]For Children and Teens SDS BMI is given. The same superscript letters indicate that there is no significant difference in BMI between the two children groups and between the two adult groups (*t*-test, both p>.05).
[a] SDS BMI, for children and teens.
[b] BMI, for adults and elderly.

consumption of a fixed amount of liquid breakfast (a commercially available vanilla (vanilla or strawberry flavour in children and teens) whey protein shake from XXL Nutrition, The Netherlands prepared with full-fat milk), 1.4 x basic metabolic rate (BMR), calculated with the Schofield equation. With this equation an individual's BMR can be estimated by using age, gender and weight (Schofield, 1984). The time between the two scan sessions was 1–2 weeks. The conditions (i.e. hungry or sated state) were counterbalanced. Upon arrival on a study morning, participants filled out several questionnaires and executed a computerized food image rating task. During this task, participants rated 133 standardized food images (Charbonnier et al., 2016). Adults rated liking, perceived caloric content and perceived healthiness on 9 point Likert scales. Children rated liking and perceived healthiness on 5 point Likert-type scales. On the sated morning session, the computerized food image rating task was executed 20 min after liquid breakfast consumption. The liquid breakfast was consumed between 7:30 and 11:00 a.m. Participants entered the scanner approximately 1 h after liquid breakfast consumption. For hormone analyses (not part of the current analysis) blood was collected in adults and elderly through a cannula on several time points during both morning sessions. Subsequently, participants underwent a 38-min MRI scan session consisting of four functional MRI runs during which they performed a food image viewing task, a food choice task (two parts) and a monetary reward task. The results of the food image viewing task are the focus of this paper. See for more details the study procedures in Fig. 1.

Food image viewing fMRI task

In the food image viewing task, participants watched 18 blocks of 7 images each (12 blocks with foods, i.e., 6 blocks with high and 6 blocks with low calorie food images; and 6 blocks with non-foods). See an example in Fig. 2. The images came from a standardized image set (Charbonnier et al., 2016) and the food images were pretested on recognizability and liking in all countries. Numbers of the images used

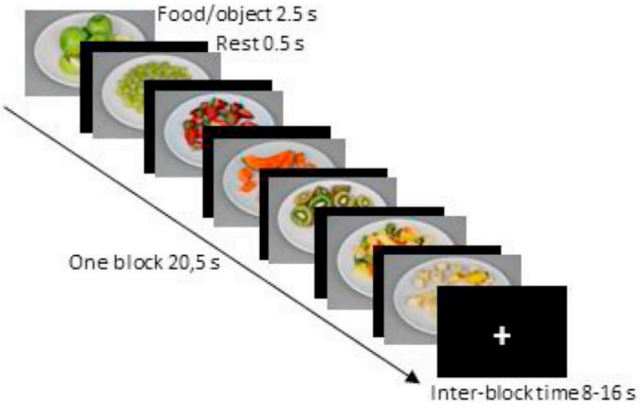

Fig. 2. Structure of the food image viewing task. Depicted is one low calorie block. The task included both low and high calorie food blocks and non-food blocks (showing images of office utensils).

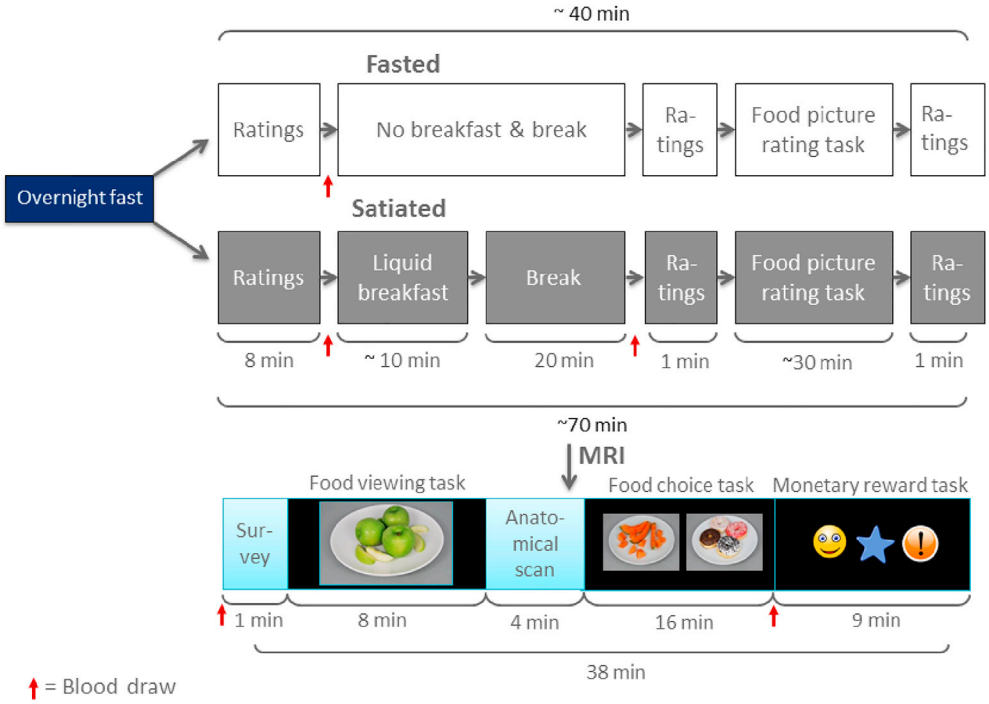

Fig. 1. Overview of all study procedures. Blood was only collected from adults and elderly. The current paper focusses on the food viewing task.

can be found in the Appendix. Each block was followed by an inter-block interval (i.e. black screen with crosshair) with a randomized duration between 8 and 16 s. In total, participants viewed 126 images over 454 s (~8 min). They were given the following task instruction: "In the next task you will see food and non-food products. Please look at the images and pay close attention, since at the end of the MRI session you will be asked a couple of questions regarding the images shown during this task." After the MRI session, participants were shown 10 images for which they had to indicate whether they had seen them during the task.

Image acquisition

In all countries imaging was performed on a Philips Achieva 3.0 T MRI scanner (Philips Healthcare, Best, NL). Functional images were obtained with an 8-channel SENSE head-coil using a 2-D echo planar imaging (EPI) sequence with the following parameters: voxel size 4 mm isotropic; repetition time (TR) = 1600 ms; echo time (TE) = 23 ms; flip angle = 72.5°; 30 axial slices; SENSE-factor $R = 2.4$ (anterior-posterior). A total of 316 functional images were acquired. A high resolution anatomical image (T_1-weighted scan) was acquired at $1 \times 1 \times 1$ mm resolution (TR/TE = 8.4/3.8 ms, total scan duration = 454 s). Data quality was monitored by regularly examining the mean functional, standard deviation and signal-to-noise ratio images for deviations.

Data analyses

Behavioral analyses

Behavioral data were analyzed with the use of SPSS Statistics 23. Hunger and fullness ratings were analyzed by using four paired sample *t*-test per age group. The significance threshold was Bonferroni corrected (p = .0125; (0.05/4)). The 5-point liking ratings of children were linearly transformed to the 9-point scale of the other groups to facilitate group comparisons. The image rating task served to collect liking ratings to be able to match choice pairs in the food choice task on liking (to be reported elsewhere). Although no identical images were used in the food viewing and food choice task there was intentional overlap in the foods depicted. Using liking ratings from 23 low calorie and 23 high calorie foods shown in the food image viewing task average (changes) in liking were calculated. Effects of treatment on liking ratings were analyzed by performing a repeated measures ANOVA and Bonferroni-corrected post-hoc tests.

Image preprocessing

Image preprocessing and analyses were carried out with the SPM12 software (http://www.fil.ion.ucl.ac.uk/spm). After slice timing correction and realignment, the structural scan was coregistered to the mean functional scan. Next, the structural scan was segmented using unified segmentation, and normalization parameters were estimated. A study-specific anatomical template was created using DARTEL (Ashburner, 2007), and after coregistration DARTEL was used to normalize this template and the functional scans to MNI space (Montreal Neurological Institute–International Consortium for Brain Mapping). The data were then smoothed with an 8 mm full width at half maximum isotropic Gaussian kernel. The Volume Artefact tool from ArtRepair (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm) was used to detect and repair anomalously noisy volumes. Volumes that were moved more than 1 mm/TR were repaired. Based on this detection three children had to be excluded from analysis because of too many volumes (>30%) that had to be repaired.

Individual & group analyses

The following conditions were modelled: high calorie food image viewing, low calorie food image viewing and non-food image viewing. Subsequently, the average brain activation during food versus non-food image viewing and high versus low calorie food image viewing were calculated across conditions (mean hungry and satiated) and between conditions (hungry – satiated) for each participant. These contrast images were then submitted to ANOVAs to test for age-group and condition differences in activation during food versus non-food and high versus low calorie food image viewing. Scan order and country were added as covariates. The statistical parametric maps generated were masked with an average grey matter mask of the group and thresholded at a threshold equivalent to $p < .05$ corrected for multiple comparisons across the analysis mask. This threshold was derived using Monte Carlo simulations (10,000 iterations) of random noise distribution in the whole brain mask using the 3dClustSim function in AFNI (Cox, 1996; Forman et al., 1995). This approach combines an individual voxel probability threshold with a minimum cluster size to estimate the probability of a false positive. The resulting threshold was $p < .001$ with a cluster extent $k \geq 29$ for the food versus non-food image viewing analysis and $k \geq 30$ for the high versus low calorie food image viewing analysis. For selected significant clusters average parameter estimates were extracted for each participant with the use of the MarsBar toolbox (http://marsbar.sourceforge.net/), for establishing the direction of significant effects. For main effects of age Bonferroni-corrected posthoc t-tests were done on the average cluster parameter estimates in SPSS.

Results

Behavior

Baseline hunger and fullness ratings (measured after an overnight fast and before feeding), except for adult fullness, did not differ significantly between the study days (hungry-sated, hunger ratings: (children: $t(16) = -0.251$, $p = .805$; teens: $t(37) = 1.260$, $p = .216$; adults: $t(33) = 2.149$, $p = .039$; elderly: $t(28) = 1.386$, $p = .177$; hungry-sated, fullness ratings: children: $t(16) = -1.595$, $p = .130$; teens: $t(37) = -1.503$, $p = .141$; adults: $t(33) = -3.043$, $p = .005$; elderly: $t(28) = 0.660$, $p = .515$).

For all age groups hunger ratings prior to the scan were significantly lower on the sated day (hungry-sated: hunger ratings: (children: $t(14) = 4.365$, $p = .001$; teens: $t(33) = 7.970$, $p < .001$; adults: $t(27) = 10.842$, $p < .001$; elderly: $t(27) = 4.877$, $p < .001$), while fullness ratings were significantly higher prior to the scan on the sated day (hungry-sated: fullness ratings: children: $t(14) = -3.287$, p = .005; teens: $t(33) = -9.949$, $p < .001$; adults: $t(27) = -11.301$, $p < .001$; elderly: $t(27) = -3.156$, $p = .004$). See Table 2 for an overview.

High-low calorie food image liking ratings differed between age groups (Fig. 3, main effect group: $F(3,117) = 16.88$, $p < .001$). Children and teen's high-low calorie food liking ratings were significantly greater than those from adults and elderly ($p < .001$; children-teens: $p = .917$; children-adults: $p = .001$; children-elderly: $p < .001$; teens-adults: $p = .008$; teens-elderly: $p < .001$; adults-elderly: $p = .082$). There was no significant main effect of hunger condition ($F(1, 117) = 2.21$, p = .140) and no interaction effect ($F(3, 117) = 0.44$, p = .723). See Appendix Figure A.1).

Food versus non-food image viewing

There was no significant main effect of hunger state on food versus non-food image viewing related-brain activation. There was also no significant main effect of age group on food versus non-food image viewing activation. However, a cluster on the borders of the vermis, precuneus and lingual gyrus showed a trend for a main effect of age (Appendix Figure A.2, MNI peak coordinate: 4, −48, 8; $F = 9.18$; $Z = 4.14$; k = 28). In this region, the activation in children was lower compared to adults ($p = .001$) and elderly ($p < .001$). Activation between children and teens, and between teens, adults and elderly did not differ significantly (children-teens: $p = .135$; teens-adults: $p = .358$; teens-elderly: $p = .061$; adults-elderly: $p = 1.000$). There was no significant interaction between age group and hunger state.

Table 2
Hunger and fullness ratings in the four age groups (mean ± SD).[a]

	Children	Teens	Adults	Elderly
Hungry condition				
Hunger ratings				
Baseline	3.1 ± 0.8	5.9 ± 2.5	6.7 ± 1.72[b]	4.7 ± 2.1[h]
20 min after drink	n.a.	n.a.	n.a.	n.a.
Prior to scan	4.1 ± 0.8[g]	6.8 ± 2.0[f]	7.4 ± 1.2[c]	5.1 ± 2.1[h]
Fullness ratings				
Baseline	1.6 ± 0.6	2.7 ± 1.8	2.2 ± 1.4[b]	3.5 ± 1.7[h]
20 min after drink	n.a.	n.a.	n.a.	n.a.
Prior to scan	1.7 ± 0.8[e]	2.7 ± 1.6[f]	1.9 ± 1.4[c]	3.0 ± 1.6[h]
Sated condition				
Hunger ratings				
Baseline	3.3 ± 1.1	4.4 ± 2.1	6.1 ± 1.6[b]	5.4 ± 2.4[h]
20 min after drink	2.1 ± 0.8	2.8 ± 2.1	2.7 ± 1.7[b]	2.4 ± 1.6[h]
Prior to scan	2.9 ± 1.2[e]	3.6 ± 2.0[g]	3.1 ± 1.8[d]	3.7 ± 1.9[g]
Fullness ratings				
Baseline	2.1 ± 0.8	3.3 ± 1.8	2.9 ± 1.4[b]	3.2 ± 1.7[h]
20 min after drink	3.6 ± 0.8	5.7 ± 1.9	6.8 ± 1.7[b]	7.1 ± 1.6[h]
Prior to scan	2.6 ± 1.1[e]	4.4 ± 2.0[g]	7.0 ± 1.8[d]	6.5 ± 1.8[i]
p-values hungry vs. sated condition				
Hunger ratings				
Baseline	0.805	0.216	0.039	0.177
Prior to scan	0.001*	<0.001*	<0.001*	<0.001*
Fullness ratings				
Baseline	0.130	0.141	0.005*	0.515
Prior to scan	0.005*	<0.001*	<0.001*	0.004*

*Significant difference (Bonferroni-corrected).
[a] In children 5-point Likert scales were used. In teens, adults and elderly 9-point Likert scales were used.
[b] N = 35.
[c] N = 30.
[d] N = 28.
[e] N = 17.
[f] N = 37.
[g] N = 34.
[h] N = 30.
[i] N = 28.

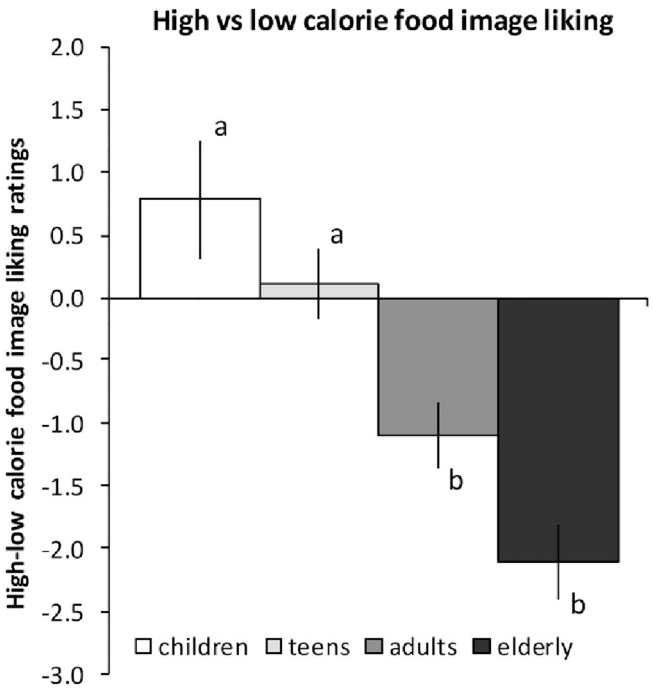

Fig. 3. Mean ± s.e.m. average high-low calorie food image liking ratings. Different letters indicate significant group differences. For example, teens (a) do not differ from children (a) but do differ from adults (b) and elderly (b).

High versus low calorie food image viewing

During high versus low calorie food image viewing there was a significant main effect of hunger state in two clusters (Table 3) covering parts of the bilateral dorsomedial and medial prefrontal cortex (dmPFC, Fig. 4), and right dlPFC (Fig. 5). In both these clusters, activation during high compared to low calorie food image viewing was greater in the hungry compared to the sated state. The difference in average food image liking between the hunger states did not significantly affect these clusters (see Appendix Table A.3 for the model without liking). Thus, the observed differences between the hunger states are not driven by differences in food image liking. There was no significant main effect of age group on high versus low calorie food image viewing and no interaction between age group and hunger state.

Discussion

To our knowledge, we were the first to examine food-related brain responses across the life span during both hunger and satiety. We found increased dmPFC and dlPFC activation during high compared to low calorie food image viewing in a hungry compared to a sated state across all age groups. We found no significant differences between age groups during high versus low-calorie food viewing and during food versus non-food image viewing. Also, there were no interactions between age group and hunger state.

Effects of age on liking

Shifts in food preferences across the life span have not been systematically investigated. However, it is quite well established that elderly people can experience loss of appetite and a decline in gustatory and olfactory function, which can lead to decreased palatability of foods (Lumbers and Raats, 2000) and a shift in preference towards foods with more intense flavors (Schiffman and Graham, 2000). In addition, fMRI studies of gustatory processing have shown aging-related changes in brain activation during the perception and rating of tastants in young, middle-aged and older adults (Green et al., 2011, 2013; Hoogeveen et al., 2015; Jacobson et al., 2010, 2017; Rolls et al., 2015). Of interest (Rolls et al., 2015), show that primary taste cortex activation by different flavors does not differ between age groups while liking does, similar to our findings for food images. However, there were neural differences between vegetable juice and orange juice and soda in young but not in elderly adults in the agranular insula, anterior middle cingulate cortex, and orbitofrontal cortex which were associated with their respective (dis) liking of vegetable juice. This provides a neural basis for understanding

Table 3
Brain regions showing a main effect of hunger state during high versus low calorie food image viewing controlling for liking differences.[a]

Region		Peak MNI-coordinate (mm)				
	k	x	y	z	*F*	*Z*
dmPFC, L (medial superior frontal gyrus)	41	−4	56	24	26.15	4.70
medial PFC (medial superior frontal gyrus)		0	60	12	18.47	3.96
dlPFC, R (superior frontal gyrus)	96	20	52	24	21.61	4.29
dmPFC, R (medial superior frontal gyrus)		4	56	24	21.12	4.24
dmPFC, R (medial superior frontal gyrus)		4	52	36	19.23	4.04

[a] ANOVA with site, scan order, gender and the average difference in liking score between the hunger and satiety day as covariates. Peaks are reported for all clusters ≥30 voxels at $p < .001$ uncorrected for multiple comparisons; L = left and R = right hemisphere. dlPFC, dorsolateral prefrontal cortex. dmPFC, dorsomedial prefrontal cortex.

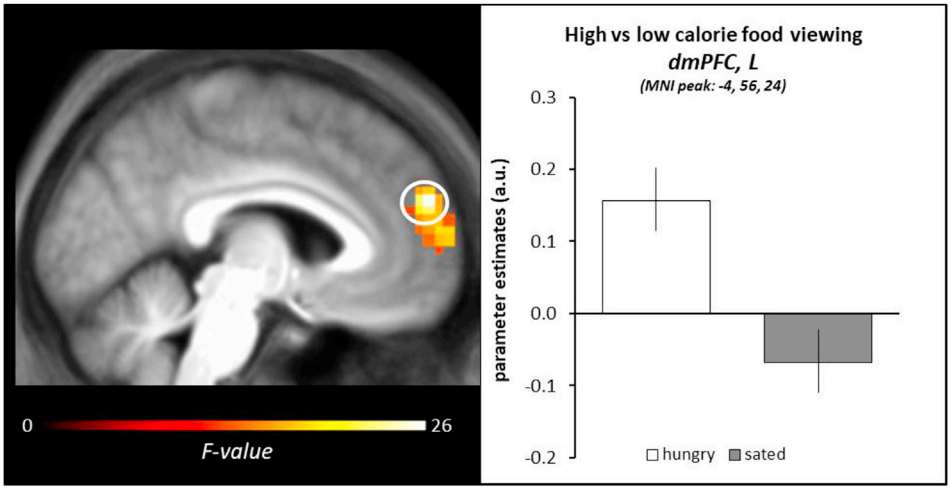

Fig. 4. Mean ± s.e.m. average dmPFC cluster parameter estimates during high versus low calorie food image viewing in the hungry and sated state (main effect hunger state). Shown is an *F*-map thresholded at $F = 11.4$, $p < .001$ uncorrected for multiple comparisons and superimposed on the mean anatomical image of all participants. The white circle indicates the peak voxel.

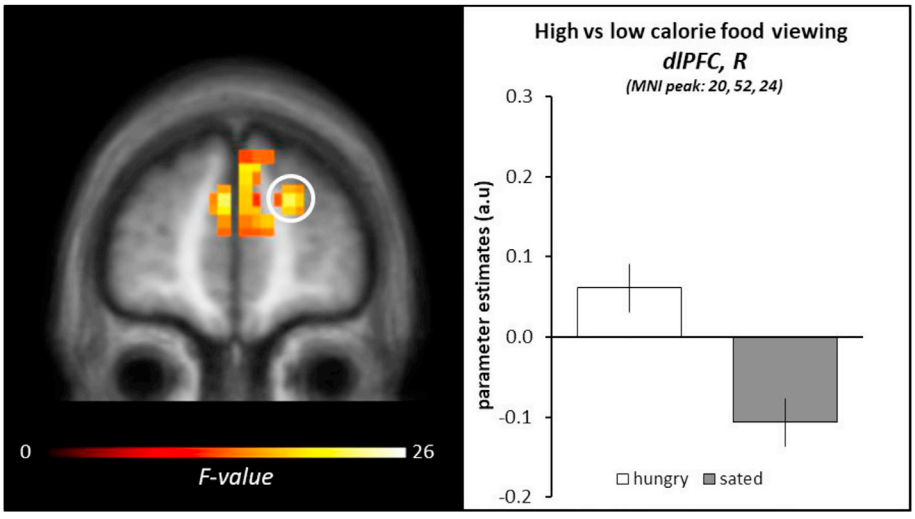

Fig. 5. Mean ± s.e.m. average dlPFC cluster parameter estimates during high versus low calorie food viewing in the hungry and sated state (main effect hunger state). Shown is an *F*-map thresholded at $F = 11.4$, $p < .001$ uncorrected for multiple comparisons and superimposed on the mean anatomical image of all participants. The white circle indicates the peak voxel.

differences in food acceptability between age groups, particularly that of sweet caloric and savory low-caloric foods.

We found that for children and teens the difference in liking between high and low calorie foods was greater than that in adults and elderly. Similarly, in our earlier study conducted with the same type of images, liking ratings tended to be higher for high calorie foods in children ($n = 191$, age 12.5 ± 2.2 y, $p = .082$) and, although not significant, in adults ($n = 449$, age 33.7 ± 13.1 y) the reverse pattern was seen ($p = .012$) (Charbonnier et al., 2016). In line with this it has been found that adolescents (12–17 y) rate high calorie food images as more palatable and desirable than low calorie food images and that they find high-calorie foods more palatable than adults do, and low calorie foods less palatable (Jensen et al., 2016). This, together with our current data suggests that there is greater appreciation of low calorie foods with increasing age, across the life span.

Food versus non-food image viewing

During food versus non-food image viewing there was a trend for an effect of age group in the vermis on the border of the lingual gyrus and precuneus, with lower activation in children compared to adults and elderly. This is in line with a meta-analysis on food image viewing brain activation that found lower lingual gyrus activation in children/adolescents (9–18 y) compared to adults (19–45 y) (van Meer et al., 2015). However, the interpretation of this age difference is not straightforward. The lingual gyrus is implicated in visual attention. Thus, one possible interpretation is that children may have had a higher attention for the non-food items (office utensils). This may occur because they do not come across these items on a daily basis and may be relatively unfamiliar with them.

Contrary to our expectations, there was no significant effect of hunger state on food versus non-food image viewing across age groups. In a meta-analysis, Van der Laan et al. (2011) found moderate concurrence in food versus non-food activation for hunger compared to satiety in the right parahippocampal gyrus/amygdala and left inferior frontal gyrus/-lateral OFC (with three and two contributing studies, respectively). However, the 5 studies included varied considerably in fasting period, among other differences. Also, unlike other studies, our food stimuli blocks consisted of 50% high and 50% low calorie food images. Most studies used high calorie palatable foods in their food versus non-food comparison, which differs substantially from the comparison we made (Beaver et al., 2006; Cascio et al., 2012; Cornier et al., 2009; Davids et al., 2010; Malik et al., 2011; Murdaugh et al., 2012; Rubinstein et al., 2011; Schienle et al., 2009; Simmons et al., 2005; Smeets et al., 2013). In addition, the non-foods used in these studies were highly variable, ranging from animals to blurred images, landscapes, non-edible food

related utensils, cars, locations and buildings, office utensils and a combination of different types of non-foods (for a complete overview see (Van der Laan et al., 2011) and (van Meer et al., 2015). The vast majority of these non-foods is very different from the non-foods we used (matched office utensils arranged to mimic the variation in color and shape of the food stimuli. This, along with a more rigorous statistical threshold, might explain why we observed no effect of hunger state on food versus non-food cue activation. This suggests that the degree of hunger we employed (overnight fast) does not significantly increase the salience of food in general across age groups. Rather, hunger effects appear to be specific for high-calorie foods, which is in line with previous studies and is also reflected in what we found for high versus low calorie foods (see below).

High versus low calorie food image viewing

To our knowledge, brain responses to high versus low calorie food image viewing have not been compared between hungry and satiated states across the life span. We expected lower activation in frontal areas such as the dlPFC in children, teens and elderly compared to adults, especially when sated. We also expected heightened responses in reward-related areas in adolescents and a decline from adulthood into senescence. However, what we found was an effect of hunger state across age groups for high versus low calorie food image viewing and no interaction between hunger state and age; the bilateral (dorso)medial PFC and right dlPFC showed increased activation during the fasted compared with the sated state.

Only a very minor part of the activation differences found in these areas could be attributed to differences in food liking between the hunger states. The (ventro)medial PFC encodes the reward value of reinforcers such as food cues (Kringelbach and Rolls, 2004). Thus, our findings might suggest that hunger specifically increases the reward value of high calorie foods irrespective of age, and that this effect is not driven by changes in liking, which is one of the factors contributing to reward value. Thus, our assumption that our high-energy foods would elicit similar anticipatory responses as monetary reward cues across age groups did not hold. One reason for this may be that food images do not signal acute reward delivery. However, in a study in adolescents with both food (milkshake) and monetary reward anticipation and receipt there was also no overlap in the areas activated during reward anticipation (Stice et al., 2011).

The dlPFC has been implicated in top-down and cognitive control (Carter and Van Veen, 2007), self-control during food choices (Hare et al., 2009, 2011), and response inhibition (Simmonds et al., 2008). Moreover, there is evidence that food viewing can elicit activation of brain regions involved in inhibitory control (Bruce et al., 2010; Davids et al., 2010; Killgore et al., 2003; Smeets et al., 2013; Stice et al., 2008). We found deactivation for HC versus LC food image viewing during satiety in the right dlPFC. In a meta-analysis of food versus non-food viewing during hunger versus satiety, varying in time since last meal, there was no concurrent effect in the dlPFC (see above), while there was a concurrent cluster in the left dlPFC for high-energy versus low-energy food image viewing, albeit with only two contributing studies (Van der Laan et al., 2011). Hare et al. (2011) found effects of perceived healthiness of food images in two parts of the left dlPFC during food decision-making, i.e., in a task which is better suited to engage inhibitory control processes than a passive viewing task. This may seem in contrast with our right dlPFC finding. However, in Go/No-go tasks requiring frequent updating of stimulus–response associations in working memory and actual response inhibition, consistent right dlPFC activation is observed (Simmonds et al., 2008). Moreover, van Meer et al. (2016b) report a negative correlation between BMI and unhealthy versus healthy food image viewing in 10–12 y-old children but not adults, in a left dlPFC ROI, but most prominently in the right dlPFC. This cluster overlaps with our right dlPFC cluster showing a main effect of hunger. This suggests that high-calorie foods may trigger inhibitory control-related processes during hunger.

In line with our results, increased activation in the dorsomedial and lateral PFC has been reported during a hungry compared with a sated state in lean and obese children during food vs non-food viewing (Bruce et al., 2010) and in normal-weight adults during high versus low calorie food viewing (Goldstone et al., 2009). Overall, these and our results could thus reflect increased reward value for (high) calorie foods and concomitant engagement of cognitive control processes during hunger, which we show is irrespective of age. This would require confirmation in future studies that include explicit behavioral measures of inhibitory control.

Limitations

International multi-center fMRI studies carry a risk of confounding effects due to differences between scanners and other differences between sites such as (eating) culture which cannot be disentangled. We ensured that the same brand and type of scanner was used, allowing us to use the same scan sequence at all sites, thus minimizing scanner effects. A limitation of the present study was the unequal distribution of the age groups across sites, which is an additional confounding effect of site. In particular, all children were scanned in The Netherlands. We sought to account for this as best we could by adding site as a covariate to the analyses, which should at least be sufficient to control for consistent differences between sites, such as differences in signal-to-noise ratio. It should be noted also that between-center variability in fMRI results has been shown to be small relative to between-subject and between-visit variability when the same protocol is followed at all scanning sites (Gountouna et al., 2010; Suckling et al., 2008). Taken together, the above suggests that we can reasonably assume that our results are not overly biased by site differences, although there is still a risk that they might be biased towards a Dutch population, since the majority of participants was measured in The Netherlands. This is supported by the fact that running the analyses without the site covariates had only very minor effects and did not significantly affect the outcomes.

Conclusion

Overall, we can conclude that the effect of hunger state on the brain response to visual high-calorie food cue exposure is similar across the life span. Increased activation in the (dorso)medial PFC during hunger could reflect the increased reward value of high calorie foods across age groups due to the overnight fast. Additionally, increased dlPFC activation during hunger might reflect a greater inhibitory response to high calorie foods. This may underlie the ability to resist overconsumption of such foods in our population of normal weight individuals. Age differences in brain reactivity to (high-calorie) food cues were virtually absent and age did not interact with hunger state, suggesting that the impact of hunger state on visual food cue reactivity is similar across the life span. Future studies should further investigate these findings and include overweight and obese individuals.

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Appendix

Numbers of the food images used from the Full4health Image collection (Charbonnier et al., 2016):

1	3	4	13	18	24	30	32	33	35	37	38	42
44	50	67	69	89	100	101	104	105	106	110	111	112
115	117	118	120	121	122	125	127	128	131	132	136	140
141	142	143	144	145	146	148	149	151	152	153	157	158
159	160	161	162	163	165	166	167	168	170	171	172	17
175	176	177	178	180	181	182	183	184	189	192	204	206
220	228											

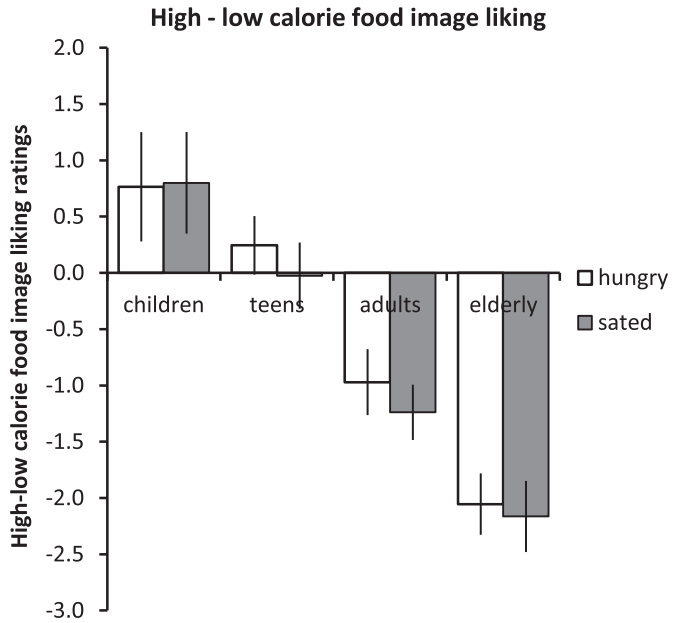

Fig. A 1. Mean ± s.e.m average difference in liking ratings (9-point scale) of high- and low-calorie food images during hunger and satiety for all age groups.

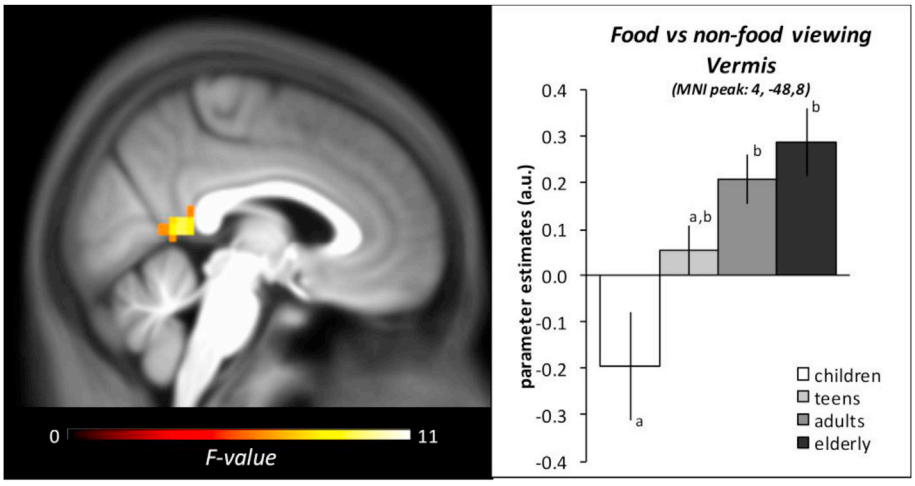

Fig. A 2. Mean ± s.e.m. average vermis cluster parameter estimates during food versus non-food image viewing in the different age groups, across hunger states (main effect age group). Shown is an *F*-map thresholded for visualization at $F = 6.0$, $p < 0.001$ uncorrected for multiple comparisons and superimposed on the mean anatomical image of all participants. In the graph, different letters indicate significant group differences as determined with Bonferroni-corrected post-hoc t-tests in SPSS. For example, children (a) do not differ from teens (a) but do differ from adults (b) and elderly (b).

Table A 3
Brain regions showing a main effect of hunger-state during high versus low calorie food image viewing without controlling for liking.[a]

Region	*k*	Peak MNI-coordinate (mm)				*Z*
		x	y	z	*F*	
dmPFC, L (medial superior frontal gyrus)	147	−4	56	24	27.06	4.78
dlPFC, R (superior frontal gyrus)		20	52	24	21.72	4.30
medial PFC (medial superior frontal gyrus)		−4	60	12	19.41	4.07
medial PFC (medial superior frontal gyrus)		4	60	12	19.30	4.05
dmPFC, R (medial superior frontal gyrus)		4	52	36	19.84	4.11

[a] ANOVA with site, scan order and gender as covariates. Peaks are reported for all clusters ≥30 voxels at $p < .001$ uncorrected for multiple comparisons; L = left and R = right hemisphere. dlPFC, dorsolateral prefrontal cortex. dmPFC, dorsomedial prefrontal cortex.

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