# Pubertal Development and Body Mass Index are associated with Dorsolateral Prefrontal Cortex Activation in Response to Unhealthy Food Cues

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**Abstract**

Unhealthy food cues are omnipresent and promote overconsumption. Although childhood obesity rates are increasing, there is no strict regulation of the marketing of unhealthy foods towards children. This is problematic since children's brains, especially areas important for cognitive control, do not mature until their early 20s. It is not known in how far the brain response to unhealthy food cues varies with body mass index and age. To investigate this, 168 children (10-17 y; 71 prepubertal children, 97 pubertal children) and 182 adults (30-67 y) from the European IDEFICS cohort were scanned with fMRI while viewing pictures of healthy and unhealthy foods. Pubertal children exhibited lower activation in the right dorsolateral prefrontal cortex (dlPFC) compared to adults when exposed to unhealthy food cues. Across all age groups, individuals with higher body mass demonstrated reduced activation in the middle cingulum in response to unhealthy food stimuli. Lastly, the relation between body mass index and brain activation in response to unhealthy compared with healthy food stimuli varied with development: in prepubertal children, higher body mass index was correlated with decreased activation in right anterior insula and right dlPFC, whereas no such relationship was observed in pubertal children or adults. These findings suggest that pubertal children and prepubertal

children with higher body mass index may be particularly vulnerable to unhealthy food cues. In this light, the lack of regulation regarding unhealthy food marketing targeted at is concerning, especially considering the global increase in obesity rates.

## 1. Introduction

The constant exposure to unhealthy foods in modern society is thought to be a major contributing factor to the worldwide rise in obesity (Lawrence et al., 2012). Children may be more susceptible to unhealthy food cues than adults, as they were shown to have heightened attention for these cues (Soetens & Braet, 2007; Werthmann et al., 2015) and a lower ability to inhibit their responses towards them (Junghans et al, 2015). The combination of higher attention and lower inhibition may make children more sensitive to unhealthy food cues encountered in food marketing than adults are. Nevertheless, there has been little government regulation to limit the marketing of unhealthy foods targeting children (Lobstein et al., 2015). There have been several industry-led pledges aimed at limiting food advertising directed at children under the age of twelve, such as the EU-pledge (EU Pledge, 2023) in Europe and the Children's Food & Beverage Advertising Initiative (Enright & Eskenazi, 2022) in North America. However, these voluntary food industry initiatives are frequently criticized because of weak standards and commitments, and a lack of both transparency and enforcement mechanisms (Swinburn et al, 2015; Bryden et al., 2013; Hawkes & Harris, 2011; Galbraith-Emami & Lobstein, 2013).

Children’s increased susceptibility to unhealthy food cues may be explained by their brains still developing, a process that continues until the early twenties (Booth et al., 2003). Not all brain

areas mature at the same rate; between age 8 and 21 greater changes have been found in the prefrontal cortex (PFC) relative to other brain regions for synaptogenesis (Huttenlocher & Dabholkar, 1997), gray matter reduction (Sowell et al., 1999), myelination increases (Giedd et al., 1999) and resting level metabolism. Examining how children's brains respond to food cues may shed light on the mechanism behind their increased susceptibility. This is important, since brain reactivity to food cues in reward related areas predicted future weight gain in adolescent girls (Yokum & Stice, 2011), and women (Demos et al., 2012) as well as food choice (Van der Laan et al., 2012; Mehta et al., 2012), snack consumption (Lawrence et al, 2012), weight status in women (Killgore et al., 2013), and outcome in a weight-loss program (Murdaugh et al., 2012). However, very little is known about how these neural responses towards foods change over the course of adolescence, i.e., in the transition from child to adolescent to adulthood. An activation-likelihood estimation meta-analysis indicated that children may have lower activation in the lingual gyrus, a visual processing area, in response to food cues (van Meer et al., 2015). This meta-analysis included studies with a wide age range of children (8-18 years old) and compared these with studies in adults. Another study showed that children (10-12 years old) had stronger activation in response to unhealthy foods compared to adults in a brain area involved in motivated action, the precentral gyrus (Van Meer et al., 2016). While these studies offer intriguing insights into how children's and adults' brain responses to food cues differ, the developmental trajectory of these brain responses remains unclear.

Another factor that may influence children's susceptibility to unhealthy food cues is their body mass index (BMI). Several studies suggest that children with a higher body mass index have altered brain responses to (unhealthy) food cues, although the direction of these effects vary

between studies (Davids et al., 2010; Bruce et al., 2010; Yokum & Stice, 2011; Stice et al., 2008; Van Meer et al., 2016; Batterink et al., 2010). It is unknown in how far the brain responses to food cues vary with body mass index in children and adults in the same way. A recent review and meta-analysis found differences between individuals with overweight/obesity and individuals with normal weight in the left insula and left fusiform gyrus in response to viewing food vs. non-food pictures (Morys et al., 2023). However, the group differences in both these regions were age dependent: in children there were weight group differences in left insula activation but less so in older adults, while in adults there was a bigger weight group difference in fusiform gyrus activation than in children. These findings suggest that the relationship between body mass index and food cue reactivity may be age dependent, but given the modest sample size of the studies included and the fact that the average age per participant group was used to study the effect of age, a more thorough examination is warranted.

In the present study, we aimed to determine in how far neural food cue reactivity varies with body mass index and pubertal development. We hypothesized that with the maturation of the prefrontal cortex, activation in response to unhealthy foods in areas involved in cognitive control such as the dlPFC and the ventrolateral PFC (vlPFC) will increase over adolescence, while it will decrease in the precentral gyrus (Hypothesis 1). We expected that adults still have stronger responses in the prefrontal gyrus and weaker responses in the precentral gyrus than pubertal children. Furthermore, we hypothesized that individuals with a higher body mass index will have weaker activation in response to unhealthy foods in areas involved in cognitive control (Hypothesis 2). Lastly, we hypothesized that body weight and development interact,

such that in prepubertal children the association between body mass index and activation in inhibitory brain areas will be stronger than in pubertal children or adults (Hypothesis 3).

## 2. Methods

### *2.1 Participants*

190 children (10-17 y, mean age 13.3) and 187 adults (30-67 y, mean age 44.8; the sex-matched parents of the children) in Germany, Hungary and Sweden were scanned with fMRI while they viewed healthy and unhealthy foods. Children were part of the IDEFICS/I.Family cohort; which has been described in detail elsewhere (Ahrens et al., 2016). In- and exclusion criteria were the same as van Meer et al. (2019). All children provided assent and their parents provided written informed consent for themselves and their children before participation, as approved by the Scientific and Research Ethics Committee of the Medical Research Council of Pécs (TUKEB), the Ethics Committee of the University of Bremen and the Regional Ethics Committee of the University of Gothenburg. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The data of 22 children and 5 adults could not be used for analysis, because of excess movement (n=16 children), missing weight and height measurement on the scan day (n=3 adults) or insufficient scan quality (n=8 children, n=2 adults). This left a final sample of 168 children and 182 adults (see Table 1 for demographics). The pubertal stage of the children was assessed based on menarche in girls and the onset of voice change in boys (Carskadon & Acebo, 1993). There were 71 prepubertal children and 97 pubertal children. There were no statistically significant differences in the number of boys and girls per child group (prepubertal and pubertal; ($t(166) = 1.34$, $p = 0.18$).

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Table 1: Mean (SD or %) of demographic variables per age group

| | Prepubertal children (n=71) | | | Pubertal children (n=97) | | | Adults (n=182) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Range | Mean | SD | Range | Mean | SD | Range |
| Sex (n, %)[1] | 44 F (62%) | | | 50 F (51.5%) | | | 96F (52.5%) | | |
| Age (y) | 11.8 | 1.15 | 9.9-14.6 | 14.5 | 1.29 | 11.42-17.42 | 44.8 | 5.2 | 30-67 |
| (SDS) BMI[2] | 0.23 | 0.91 | -1.40-2.87 | 0.56 | 1.02 | -2.83-2.87 | 26.9 | 5.37 | 17.6-46.8 |

[1]The number of boys and girls did not statistically significantly differ between the children groups.
[2]BMI in kg/$m^2$ is reported for adults, BMI standard deviation score (SDS BMI) is reported for children based Cole & Lobstein (2012). F = female

### *2.2 Study procedures*

In a visit prior to the scan, children were familiarized with the study procedures. Participants were asked not to eat or drink anything (except water) for the two hours before the scan. At arrival, their height and weight were measured. This was followed by the scan session, in which participants completed a food choice and food viewing task (in this order) in the MRI scanner. Only the results of the food viewing task are presented in this paper, results of the food choice task in children have been reported elsewhere (Van Meer et al., 2019). After the scan, participants were asked to rate the healthiness and tastiness of a subset of the pictures of the food viewing task (80%) on a five-point scale (*How much do you like the product?* 1, *not at all* – 5, *very much*; *How healthy do you think the product is?* 1, *not healthy at all* – 5, *very healthy*) in a computerized rating task.

### *2.3 Food viewing fMRI task*

The food viewing task (8-min; as used in Van Meer et al., 2016) consisted of 8 blocks of healthy and 8 blocks of unhealthy food pictures with 8 pictures per block (block duration 24 s; total number of pictures 128; no repetitions). Blocks of healthy and unhealthy pictures were alternated in the same order for all participants. Picture presentation lasted 2.5 s with a 0.5 s inter-stimulus interval. Between blocks a crosshair was presented for 3 to 9 s. Stimuli were presented on a screen (viewed via a mirror) or on goggles with use of the PRESENTATION software (Neurobehavioral Systems Inc., Albany, CA, USA). Participants were told that a picture recall test would follow after the scan, so they had to pay attention to the food pictures in the task. Standardized food pictures from the Full4Health Image Collection (Charbonnier et al., 2016) were used as stimuli. To quantify the healthiness of the foods used the Nutrient Rich Food (NRF) index (Drewnowski, 2010) was utilized. Because of local differences in food familiarity a different set of pictures was used in each country. The mean NRF index was 149.3 (SD 235.8) in Germany, 160.0 (SD 243.8) in Hungary and 159.4 (SD 236.2) in Sweden for the pictures in healthy blocks and -3.9 (SD 10.3) in Germany, -1.6 (SD 11.6) in Hungary and -3.7 (SD 10.7) in Sweden for the pictures in unhealthy blocks.

### *2.4 Rating analysis*

In order to compare the difference between the age groups in taste and health ratings for the pictures in the healthy and unhealthy blocks, t-tests, paired t-tests and ANOVA's were used depending on the comparison.

### *2.5 MRI data acquisition and preprocessing*

MRI scans were conducted across three centers using 3T MRI scanners: a Siemens Skyra in Germany, Siemens Trio in Hungary (Siemens AG, Erlangen, Germany), and GE Discovery MR750w in Sweden (GE Healthcare Systems, Milwaukee, USA). A 32-channel head coil was utilized in Germany and Sweden, while Hungary employed a 12-channel head coil. A $T_1$-weighted structural image was acquired with a resolution of 1 × 1 × 1 mm, consisting of 176 sagittal slices and a field of view measuring 256 × 256. Specific acquisition parameters varied between centers. In Germany, the repetition time (TR) was 1900 ms, echo time (TE) was 2.07 ms, and the flip angle was 9°. In Hungary, TR was 2530 ms, TE was 3.37 ms, and the flip angle was 7°. In Sweden, TR was 6.928 ms, TE was 2.53 ms, and the flip angle was 7°. The functional scan employed a $T_2$*-weighted gradient echo 2D-echo planar imaging sequence with consistent parameters across sites: TR/TE of 2000/30 ms, flip angle of 76°, 36 axial slices, and voxel size of 3 × 3 × 3 mm.

Data preprocessing and analysis were carried out using SPM12 (update nr 7219), developed by the Wellcome Department of Imaging Neuroscience in London, United Kingdom, executed with MATLAB R2015b (The MathWorks Inc., Natick, MA, USA). Following slice time correction with the middle slice as reference, the functional images underwent realignment to the first volume. Subsequent steps included gray and white matter segmentation and the creation of a custom anatomical template using Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL). After coregistration, DARTEL facilitated the normalization of both the template and functional scans to MNI space (Montreal Neurological Institute–International Consortium for Brain Mapping). Further processing involved applying a 6 mm full-width at half maximum isotropic Gaussian kernel for data smoothing. The Volume Artefact tool provided by

ArtRepair (available at http://cibsr.stanford.edu/tools/human-brainproject/artrepair-software.html) was employed to identify and rectify abnormally noisy volumes. Specifically, volumes exhibiting movements exceeding 1 mm per TR were corrected. Notably, 16 children were excluded from the analysis because more than 25% of their volumes required correction.

*2.6 Subject level analyses*

For each participant, data were high-pass filtered using a 128-s cutoff and statistical maps were generated by fitting a boxcar function to the voxel time series which was convolved with the canonical hemodynamic response function (HRF). Viewing healthy foods and viewing unhealthy foods were modeled as two separate conditions. Contrast images were generated by subtracting the mean brain response during unhealthy blocks from the mean brain response during healthy blocks.

*2.7 Group level analyses*

To examine the effect of development on the brain responses to unhealthy and healthy food viewing, a one-way ANOVA was performed to compare prepubertal children, pubertal children and adults. A covariate was added for standardized BMI. This zBMI score was calculated by standardizing the children's BMI Cole SDS and the adults' BMI scores within their respective groups to a z-distribution, and then combining these standardized scores into a single variable. This ensures that the within group variation in BMI is examined and that between group variation in BMI or range differences do not play a role. Two dummy variables to encode the three countries were added as covariates of no interest in all

analyses. To determine whether the effect of BMI was dependent on development, a regression analysis was done to examine the interaction of BMI and development. Predictors were two dummy variables for group and variables for BMI per group. A cluster level threshold of $p<0.05$ Family Wise Error (FEW) corrected for multiple comparisons across the whole brain was derived using Monte Carlo simulations (10,000 iterations) of random noise distribution in the whole brain mask using 3dClustSim 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 $p<0.001$ with a cluster extent $k\geq21$ voxels.

### *2.8 Psychophysiological interaction*

As a last step, psychophysiological interaction (PPI) analysis was conducted to identify regions showing different correlation during the unhealthy compared to the healthy blocks. Methods and results are reported in the Supplemental Information.

### *2.9 Data availability*

All single-subject t-maps and group-level t-maps can be found on NeuroVault at https://neurovault.org/collections/DOWRYIVG/.

## 3. Results

### *3.1 Picture ratings*

To examine the perceived healthiness of the food pictures for prepubertal children, pubertal children and adults the healthiness ratings of a subset of the pictures in the healthy and

unhealthy blocks were compared. All groups rated a subset of the pictures in the healthy blocks as statistically significantly healthier than a subset of the pictures from the unhealthy blocks (Table 2; paired sample t-test, prepubertal children: $t(1,69) = 26.6$, $p < 0.001$; pubertal children: $t(1,95) = 39.6$, $p < 0.001$; adults: $t(1,179) = 71.8$, $p < 0.001$). However, there was an interaction between group and picture type on health rating: adults had a bigger difference in their health rating of the healthy and unhealthy pictures than children ($F(2,343) = 59.4$, $p < 0.001$). All participants provided tastiness ratings of the food pictures as well. Adults preferred the taste of the foods in the healthy blocks, while for prepubertal and pubertal children there was no difference between blocks (Table 2; paired sample t-test, prepubertal children: $t(1,69) = -0.53$, $p = 0.60$; pubertal children: $t(1,95) = 1.61$, $p = 0.11$; adults: $t(1,179) = 15.8$, $p < 0.001$). There was an interaction between group and picture type in their effect on taste rating as well: adults had a bigger difference in their taste rating of the healthy and unhealthy pictures than prepubertal and pubertal children ($F(2,343) = 59.4$, $p < 0.001$).

Table 2: Mean and SD of food picture ratings per age group

| | Prepubertal children (n=71) | | Pubertal children (n=97) | | Adults (n=182) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| Health rating healthy foods | 4.06 | 0.45 | 4.17 | 0.36 | 4.24 | 0.31 |
| Health rating unhealthy foods | 2.21 | 0.48 | 2.11 | 0.46 | 1.70 | 0.46 |
| Taste rating healthy foods | 3.71 | 0.61 | 3.85 | 0.62 | 4.10 | 0.48 |
| Taste rating unhealthy foods | 3.75 | 0.64 | 3.72 | 0.60 | 3.22 | 0.64 |

### *3.2 Brain responses to unhealthy and healthy foods*

In order to test Hypothesis 1 and examine differences in the brain responses to unhealthy compared to healthy foods between prepubertal children, pubertal children and adults a one-way ANOVA was done. There was an effect of group in the right opercular and triangular part of the inferior frontal gyrus and the right middle frontal gyrus (dlPFC; Table 3 & Figure 1).

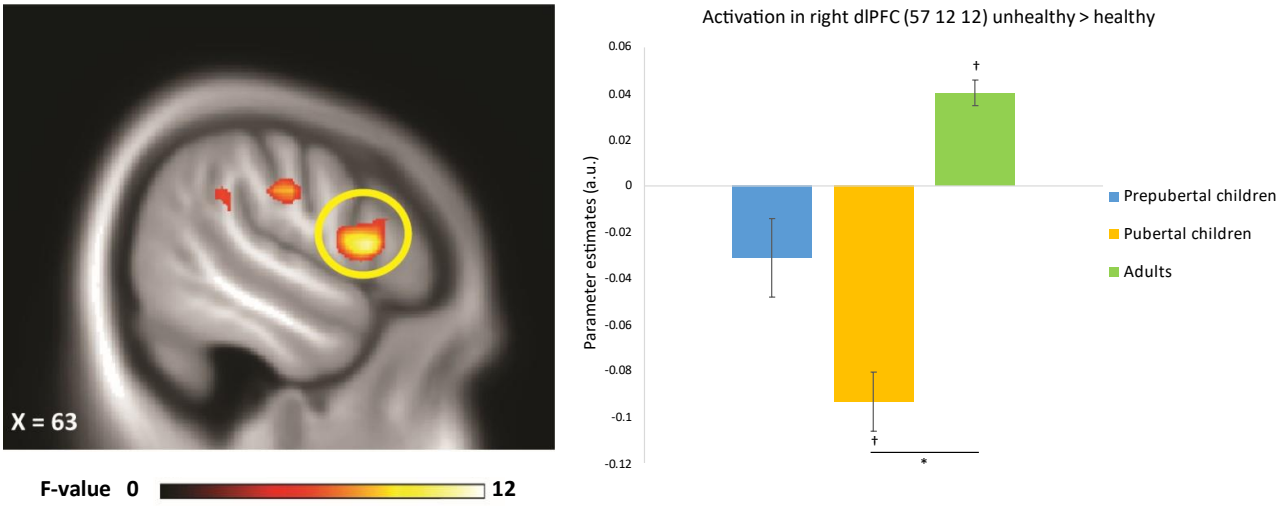


Figure 1. Group difference in the unhealthy > healthy contrast in the right dlPFC. Peaks (MNI) listed are statistically significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent threshold $k \geq 21$ , 3 × 3 x 3 mm voxels). * denotes statistically significant difference between the means of the groups, † denotes means statistically significantly differ from 0.

Post-hoc tests comparing the groups showed that in these areas, adults had stronger activation in the unhealthy compared with healthy foods contrast than pubertal children. Post-hoc analyses within the groups showed that pubertal children had stronger activation in response to healthy foods compared with unhealthy foods in these areas while adults had stronger activation in response to unhealthy foods compared with healthy foods (Table S1). In

prepubertal children there were no statistically significant differences in the response to unhealthy compared with healthy foods or vice versa in these areas.

To test Hypothesis 2 we examined whether BMI was correlated with brain responses to unhealthy compared with healthy foods over all participants. A negative correlation between zBMI and activation to unhealthy compared with healthy foods was found in the right side of the middle cingulum (Table 3).

Table 3. Brain regions that show an effect of group, zBMI or an interaction effect for unhealthy compared with healthy food viewing

| Brain region | Side | Cluster size | x | y | z | Z-value[1] |
|---|---|---|---|---|---|---|
| **Effect of group** | | | | | | |
| Inferior frontal gyrus opercular part* | R | 74 | 57 | 12 | 12 | 4.13 |
| Inferior frontal gyrus triangular part | | | 45 | 21 | 6 | 3.93 |
| Middle frontal gyrus | R | 22 | 33 | 39 | 21 | 3.73 |
| Middle frontal gyrus | | | 36 | 48 | 24 | 3.53 |
| **Negative correlation with zBMI over groups** | | | | | | |
| Middle cingulum | R | 26 | 9 | -36 | 45 | 3.78 |
| **Group differences in the correlation with zBMI** | | | | | | |
| *Linear effect of development on correlation with zBMI* | | | | | | |
| Insula* | R | 95 | 45 | 21 | -3 | 4.06 |
| Insula | R | | 42 | 15 | -2 | 3.98 |
| Insula | R | | 33 | 24 | 0 | 3.70 |
| *Children stronger negative correlation between BMI and activation than adults (post-hoc)* | | | | | | |
| Middle frontal gyrus | R | 37 | 36 | 42 | 6 | 4.15 |
| Insula* | R | 65 | 45 | 21 | -3 | 3.92 |
| Inferior frontal gyrus opercular part | R | | 54 | 18 | 6 | 3.57 |
| Insula | R | | 33 | 24 | 0 | 3.44 |

[1] Peaks (in MNI space) listed are statistically significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent threshold k ≥ 21, 3 × 3 x 3 mm voxels), * indicates $p < 0.05$ FWE corrected at cluster level; L, left; R, right.

To test Hypothesis 3 we used linear regression to examine whether there was an interaction between group and standardized BMI on the brain responses to unhealthy compared with healthy foods. Although no overall difference between the three groups was found, there was instead a linear effect of pubertal development on the correlation between standardized BMI and activation in the right anterior insula (Table 3, Figure 2). Post-hoc tests showed that there was a stronger correlation between zBMI and activation in the right middle frontal gyrus (dlPFC) and right anterior insula/frontal operculum in prepubertal children than in adults (Table 3). There were no statistically significant differences between pubertal children and adults or pubertal children and prepubertal children.

For the sake of completeness, we report the results for the unhealthy compared with healthy food viewing contrast and vice versa per group and the correlation with BMI per group in Table S1 in the Supplementary information.

Finally, PPI analyses were done to examine regions showing different correlation during the unhealthy compared to the healthy blocks and group differences and correlations with BMI. The clusters in the right dlPFC, where an effect of group was found, were used as seeds. An effect of group on the difference in connectivity with the right dlPFC (57, 12, 12) in response to unhealthy compared with healthy foods was found in the right precuneus (see Table S2). Post-hoc analyses showed that this effect was driven by a stronger connectivity in adults than pubertal children. An effect of group on the difference in connectivity with the right dlPFC (33, 39, 21) in response to unhealthy compared with healthy foods was found in the left rolandic operculum and left superior temporal/supramarginal gyrus. Post-hoc analyses showed that this

effect was driven by a stronger connectivity in pubertal children than prepubertal children (see Table S2).

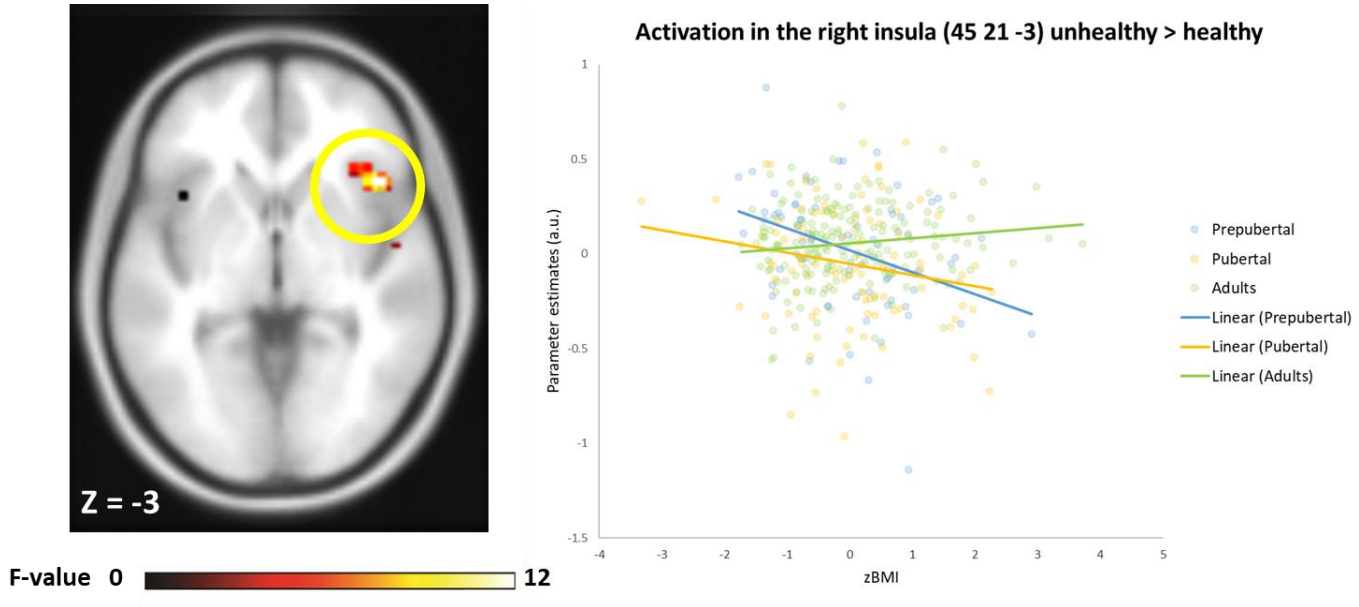


Figure 2. Group difference in the correlation with BMI and activation in the unhealthy > healthy contrast in the right anterior insula. Peaks (MNI) listed are statistically significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent threshold $k \geq 21$, 3 × 3 x 3 mm voxels).

## 4. Discussion

We examined in how far neural food cue reactivity varies with pubertal development and body mass index by comparing brain activation differences between prepubertal children, pubertal children and adults in response to viewing unhealthy and healthy food pictures. We found that pubertal children had weaker activation than adults in response to unhealthy compared to healthy food pictures in two areas in the right dlPFC. Furthermore, over the groups, standardized BMI correlated negatively with activation in response to unhealthy compared to healthy food pictures in the middle cingulum. BMI did not affect all groups to the same extent: there was a stronger negative correlation between BMI and activation in response to unhealthy

compared with healthy foods in prepubertal than adults in the right anterior insula and the right dlPFC.

*Association with pubertal stage*

Contrary to our Hypothesis 1, brain activation in inhibitory areas in response to unhealthy foods did not increase over adolescence. In fact, activation of the dlPFC, an area involved in inhibition, was higher in response to viewing healthy compared with unhealthy food pictures in both groups of children. Although there was no difference in activation between prepubertal children and adults, for pubertal children activation in the right dlPFC was stronger when viewing healthy compared to unhealthy foods, but for adults activation was stronger when viewing unhealthy compared to healthy foods. In contrast, in prepubertal children there was no difference in dlPFC activation between unhealthy and healthy food pictures. Previous studies have found both linear positive associations between development and dlPFC activation in response to rewarding cues (Giuliani & Pfeifer, 2015; Martin et al., 2019) and non-linear positive associations (Somerville et al., 2010). A study in adolescents showed that testosterone levels correlated negatively with dlPFC activation during a reward task and in girls estradiol was related to weaker connectivity between dlPFC and nucleus accumbens (Poon et al., 2019). This is in line with our findings that pubertal children seem to have lower dlPFC activation than prepubertal children in response to unhealthy food cues. Crone and Steinbeis (2017) suggested that the effects of development on dlPFC activation depend on the task. For tasks that depended on complex deliberative processes, dlPFC activation increased linearly over childhood to adulthood, while for more stimulus-driven tasks both increases and decreases in activation were found in different parts of the dlPFC. They suggest that this may reflect a

difference in strategy use (Crone & Steinbeis, 2017). The current study involved passive viewing (cue exposure) with instructions to pay attention due to a later recall task. This task could be viewed as stimulus-driven and so the differences in the activation of the dlPFC between pubertal children and adults may indicate different strategies for sustained attention or memory. However, it is difficult to determine this conclusively without a more explicit performance aspect to the task. However, studies using food choice paradigms have consistently shown the involvement of the dlPFC in food choice, with several relating higher dlPFC activation to healthier choices (Chen et al., 2018; van Meer et al., 2019; Petit et al., 2016). The dlPFC has been implicated in cognitive control, appetite regulation and response inhibition (Hare et al., 2011; Fregni et al., 2008, Menon et al., 2001). Recently, the question has been raised whether dlPFC activation in response to rewarding stimuli reflects cognitive control or rather value-based evidence accumulation (Hutcherson & Tusche, 2022). Taken together, pubertal children have lower right dlPFC activation in response to unhealthy food cues than adults. This could be due to increases in circulating sex hormones, brain development and changes in strategies deployed in stimulus-driven tasks. In light of the previous findings emphasizing that stronger dlPFC activation is related to healthier food choices, regardless of whether this reflects cognitive control or evidence accumulation, the stronger dlPFC activation during our task may indicate a greater susceptibility to unhealthy food cues especially for pubertal children. PPI analyses showed differences in connectivity between the right dlPFC clusters and areas involved in visual processing and attention (precuneus, rolandic operculum, superior temporal/supramarginal gyrus). This underscores the effect development may have on the processing of unhealthy food cues. Contrary to our hypothesis and previous findings (van

Meer et al., 2016), we did not find an association between development and precentral gyrus activation in response to unhealthy compared with healthy foods.

*Association with body mass index*

Body mass index was negatively correlated with activation in the middle cingulum in response to unhealthy compared to healthy foods, which aligns with previous work in which individuals with obesity had lower activation than individuals with normal weight in the middle cingulum in response to food compared with non-food images (Dimitropoulos et al., 2012). Previous research has highlighted the role of the middle cingulate gyrus in representing reward value as opposed to saliency (Litt et al., 2011). Activation in the middle cingulate gyrus has been found to be stronger in hungry than satiated states (Holsen et al., 2005) and stronger activation in response to high calorie compared with low calorie foods has been described in this area (English et al., 2017). More generally, the middle cingulum has an important role in attentional control (see Bubb et al., 2018 for a review). Taken together, this could indicate that lower activation in the middle cingulum in individuals with a higher BMI in response to unhealthy food pictures reflects altered reward value or attentional control towards unhealthy foods. In contrast to Hypothesis 2, higher body mass index was not related to lower activation in inhibitory areas in response to unhealthy compared to healthy food cues across age groups.

*Effect of body mass over the course of pubertal development*

In accordance with Hypothesis 3, the association between body mass and brain activation in response to unhealthy compared with healthy foods depended on development. The correlation between body mass index and right anterior insula activation in response to

unhealthy foods changed linearly over development: prepubertal children had a negative correlation between body mass and activation and right insula activation while this correlation was no longer there for pubertal children and adults. This is in line with Morys et al. (2023), who found in their meta-analysis that the correlation between body mass and insula activation became weaker with increased age (although they found this in the left insula). The insula is involved in taste processing and interoceptive awareness, i.e. the cognitive-emotional processing of bodily states, such as hunger/appetite signals from the body (Brooks et al., 2013). Additionally, comparisons between the groups showed a statistically significant difference in the dlPFC between prepubertal children and adults: in prepubertal children body mass correlated negatively with right dlPFC activation in response to unhealthy compared to healthy foods while in adults there was no correlation. Our previous study using the same task in a separate group of children and adults similarly found a negative correlation between body mass and dlPFC activation in children, but not adults (van Meer et al., 2016). Many studies have reported lower dlPFC activation in overweight and obesity (see Gluck et al., 2017 for a review; although a recent meta-analysis found no such differences (Morys et al. 2023). Adolescents who successfully maintained weight loss had stronger activation in the right dlPFC in response to viewing high- compared to low calorie foods (Jensen & Kirwan, 2015). In sum, right anterior insula and right dlPFC activation in response to unhealthy foods was correlated with body mass in prepubertal children but not pubertal children and adults. The negative correlation between body mass and anterior insula activation in response to unhealthy foods became linearly weaker over the development groups. This suggests that prepubertal children with higher body mass may be more susceptible to unhealthy food cues.

*Strengths, limitations and future directions*

The current study was performed in a large sample of 350 individuals over three European countries with a wide range of body mass. The design of including children and their parents ensures a gap between the children and adult groups, since the oldest child was 17 and the youngest adult 30. However, this could also be viewed as a weakness, since changes between 18 and 30 are unknown, and there is no such gap between the prepubertal and pubertal children. Ideally, future studies should have a longitudinal instead of a cross-sectional design to better untangle development over time from between person differences.

*Conclusions*

We determined the associations between pubertal development and body mass with neural reactivity to unhealthy food cues. Pubertal children had less activation in an area involved in cognitive control than adults in response to unhealthy foods. Across all developmental groups, individuals with a higher body mass had less activation in an area involved in attention and attentional control in response to unhealthy foods. Finally, the effect of body mass was depended on development: in prepubertal children body mass correlated negatively with activation in response to unhealthy foods in areas involved in interoceptive awareness and cognitive control while no such relationships were found in pubertal children or adults. Taken together, pubertal children and prepubertal children with a higher body mass index may be more susceptible to unhealthy food cues. This observation is particularly relevant given the absence of regulations governing unhealthy food marketing directed at children over the age of twelve (EU Pledge, 2023; Enright & Eskenazi, 2022). This is concerning in light of the rising

425 global prevalence of obesity. The implications of these findings underscore the importance of
426 addressing the possible influence of unhealthy food cues on vulnerable populations, especially
427 during critical developmental stages, to mitigate their adverse impact on public health.

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*Floor van Meer:* Formal analysis, Writing - Original Draft, Project administration. *Laura N. van der Laan:* Supervision, Writing - Review & Editing. *Gabriele Eiben*: Investigation, Resources, Writing - Review & Editing. *Lauren Lissner*: Resources, Funding acquisition, Writing - Review & Editing. *Maike Wolters*: Investigation, Resources, Writing - Review & Editing. *Stefan Rach*: Investigation, Resources, Writing - Review & Editing. *Manfred Herrmann:* Investigation, Resources, Writing - Review & Editing. *Peter Erhard:* Investigation, Resources, Writing - Review & Editing. *Denes Molnar:* Funding acquisition, Resources, Writing - Review & Editing. *Gergely Orsi:* Investigation, Resources, Writing - Review & Editing. *Roger A.H. Adan:* Funding acquisition, Supervision, Writing - Review & Editing. *Paul A.M. Smeets:* Conceptualization, Funding acquisition, Supervision, Writing - Review & Editing.

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Supplementary information

Supplementary Methods

**Psychophysiological Interaction (PPI)**

PPI analysis was conducted to identify regions showing different correlation during the unhealthy compared to the healthy blocks. The specific coordinates in the right dlPFC (57 12 12 and 33 39 21) were determined based on the effect of group on the difference between brain responses to unhealthy compared with healthy blocks. All analyses were done for both dlPFC clusters. First, for each participant, the BOLD time-series within an 8-mm sphere centered on the dlPFC ROI was extracted. Second, a general linear model was estimated for each participant, incorporating three regressors: the interaction between neural activity in the right dlPFC and the difference between unhealthy and healthy blocks convolved with the canonical HRF, the difference between unhealthy and healthy blocks convolved with the HRF and the extracted time-series from the dlPFC. Single-subject contrasts were then calculated after estimating the general linear model.

Third, group-level contrast images were generated based on the single-subject contrast values using one-sample t-tests, and group differences were examined one-way to compare prepubertal children, pubertal children and adults. A covariate was added for standardized BMI.

## Supplementary Results

Table S1. Brain regions that show an effect for unhealthy compared with healthy food viewing per group and correlation with (z)BMI

| Brain region | Side | Cluster size | x | y | z | Z-value |
|---|---|---|---|---|---|---|
| **Prepubertal children** | | | | | | |
| *Unhealthy > Healthy* | | | | | | |
| Middle occipital gyrus | R | 1238 | 33 | -81 | 9 | 7.61 |
| Inferior temporal gyrus | R | | 48 | -63 | -9 | 7.15 |
| Middle occipital gyrus | R | | 30 | -69 | 27 | 6.88 |
| Inferior occipital gyrus | L | 1724 | -42 | -69 | -3 | 7.21 |
| Inferior temporal gyrus | L | | -45 | -60 | -9 | 7.01 |
| Superior occipital gyrus | L | | -24 | -87 | 24 | 6.68 |
| Precentral gyrus | R | 156 | 42 | 3 | 30 | 5.53 |
| Postcentral gyrus | R | | 51 | -9 | 33 | 3.89 |
| Postcentral gyrus | R | | 60 | -6 | 39 | 3.44 |
| Hippocampus | R | 147 | 15 | -9 | -12 | 5.04 |
| Hippocampus | R | | 24 | -3 | -18 | 4.49 |
| Lingual gyrus | R | | 15 | -36 | -3 | 4.32 |
| Postcentral gyrus | L | 120 | -48 | -9 | 54 | 3.99 |
| Precentral gyrus | L | | -42 | 0 | 33 | 3.83 |
| Postcentral gyrus | L | | -45 | -12 | 39 | 3.66 |
| *Negative correlation with zBMI* | | | | | | |
| Middle frontal gyrus | R | 23 | 36 | 45 | 6 | 4.01 |
| Insula | R | 32 | 45 | 21 | 0 | 3.76 |
| Inferior frontal gyrus opercular part | R | | 54 | 18 | 6 | 3.40 |
| **Pubertal children** | | | | | | |
| *Healthy > Unhealthy* | | | | | | |
| Middle frontal gyrus | L | 118 | -39 | 39 | 24 | 5.20 |
| Middle frontal gyrus | L | | -27 | 33 | 24 | 4.13 |
| Middle frontal gyrus | R | 183 | 33 | 42 | 21 | 5.16 |
| Middle frontal gyrus | R | | 39 | 36 | 33 | 4.12 |
| Middle frontal gyrus | R | | 27 | 57 | 27 | 4.07 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Supramarginal gyrus | R | 325 | 63 | -30 | 27 | 4.44 |
| Rolandic operculum | R | | 60 | -18 | 15 | 4.27 |
| Supramarginal gyrus | R | | 54 | -39 | 33 | 4.12 |
| Inferior frontal gyrus opercular part | R | 52 | 57 | 12 | 9 | 4.23 |
| Middle cingulum | R | 44 | 6 | -33 | 45 | 4.21 |
| Precuneus | R | 78 | 9 | -60 | 51 | 4.13 |
| Precuneus | R | | 3 | -51 | 57 | 3.54 |
| Supramarginal gyrus | L | 127 | -63 | -36 | 30 | 3.88 |
| Supramarginal gyrus | L | | -54 | -21 | 24 | 3.78 |
| Middle temporal gyrus | L | | -54 | -48 | 24 | 3.77 |
| Middle frontal gyrus | R | 60 | 27 | 9 | 45 | 3.74 |
| Middle frontal gyrus | R | | 27 | 24 | 45 | 3.55 |
| Superior frontal gyrus | R | | 21 | 15 | 54 | 3.41 |
| Middle temporal gyrus | L | 25 | -57 | -54 | 0 | 3.68 |
| *Unhealthy > Healthy* | | | | | | |
| Middle occipital gyrus | R | 452 | 33 | -84 | 15 | 6.51 |
| Inferior temporal gyrus | R | | 48 | -60 | -9 | 5.96 |
| Middle occipital gyrus | R | | 27 | -72 | 30 | 4.93 |
| Middle occipital gyrus | L | 183 | -39 | -87 | 9 | 4.91 |
| Inferior occipital gyrus | L | | -36 | -78 | -3 | 4.44 |
| Middle occipital gyrus | L | | -33 | -90 | 18 | 4.42 |
| Fusiform gyrus | R | 68 | 30 | -45 | -15 | 4.57 |
| Fusiform gyrus | R | | 30 | -60 | -3 | 3.48 |
| Hippocampus | R | 26 | 21 | -3 | -18 | 4.09 |
| **Adults** | | | | | | |
| *Healthy > Unhealthy* | | | | | | |
| Middle occipital gyrus | L | 32 | -12 | -99 | 3 | 6.15 |
| Precuneus | L | 84 | -6 | -57 | 57 | 4.63 |
| Thalamus | R | 53 | 21 | -39 | 15 | 4.59 |
| Thalamus | R | | 12 | -30 | 18 | 3.94 |
| Medial frontal gyrus orbital part | R | 110 | 12 | 48 | -3 | 4.52 |
| Middle cingulum | R | 298 | 6 | -36 | 45 | 4.46 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Precuneus | R | | 9 | -63 | 30 | 4.42 |
| Middle cingulum | L | | -9 | -33 | 42 | 4.26 |
| Supramarginal gyrus | L | 29 | -60 | -33 | 30 | 4.11 |
| Supramarginal gyrus | L | | -63 | -33 | 39 | 3.91 |
| *Unhealthy > Healthy* | | | | | | |
| Inferior temporal gyrus | R | 2859 | 48 | -60 | -9 | Inf |
| Middle occipital gyrus | R | | 33 | -84 | 15 | Inf |
| Middle occipital gyrus | R | | 39 | -84 | 3 | Inf |
| Inferior frontal gyrus opercular part | R | 606 | 45 | 9 | 24 | 7.34 |
| Inferior frontal gyrus triangular part | R | | 48 | 30 | 21 | 5.89 |
| Inferior frontal gyrus triangular part | R | | 54 | 21 | 15 | 4.86 |
| Insula | R | 159 | 33 | 24 | -3 | 6.30 |
| Inferior frontal gyrus orbital part | R | | 30 | 33 | -9 | 4.92 |
| Inferior frontal gyrus orbital part | R | | 45 | 24 | -6 | 4.20 |
| Supplementary motor area | L | 149 | -6 | 15 | 54 | 5.58 |
| Supplementary motor area | L | | -3 | 24 | 51 | 5.30 |
| Supplementary motor area | R | | 9 | 21 | 48 | 4.29 |
| Insula | L | 630 | -30 | 24 | 0 | 5.17 |
| Inferior frontal gyrus opercular part | L | | -42 | 6 | 27 | 4.99 |
| Precentral gyrus | L | | -45 | 0 | 45 | 4.83 |
| Medial superior frontal gyrus | L | 57 | -6 | 51 | 36 | 4.54 |
| Superior frontal gyrus | L | | -12 | 57 | 27 | 3.71 |
| Hippocampus | R | 137 | 24 | -12 | -12 | 4.43 |
| Putamen | R | | 33 | -9 | -6 | 4.38 |
| Amygdala | R | | 33 | 0 | -21 | 4.13 |
| Hippocampus | L | 36 | -21 | -9 | -18 | 4.40 |
| Paracentral lobule | R | 66 | 6 | -27 | 60 | 4.29 |
| Precentral gyrus | R | | 15 | -27 | 63 | 3.79 |
| Paracentral lobule | L | | -6 | -24 | 54 | 3.71 |
| Precentral gyrus | R | 26 | 36 | -3 | 48 | 4.15 |
| Precentral gyrus | R | | 36 | -12 | 48 | 3.44 |

[1] Peaks (in MNI space) listed are statistically significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent = 22 voxels, 3 × 3 x 3 mm voxels); L, left; R, right.

Table S2. Psychophysiological interaction with dlPFC seeds for the contrast unhealthy compared to healthy foods

| Brain region | Side | Cluster size | x | y | z | Z-value[1] |
|---|---|---|---|---|---|---|
| **Seed 57 12 12** | | | | | | |
| *Effect of group* | | | | | | |
| Precuneus* | R | 74 | 15 | -63 | 30 | 3.84 |
| Precuneus | R | | 45 | 21 | 6 | 3.93 |
| **Seed 33 39 21** | | | | | | |
| *Effect of group* | | | | | | |
| Rolandic operculum | L | 21 | -57 | 6 | 6 | 4.18 |
| Superior temporal gyrus* | L | 38 | -63 | -12 | 12 | 3.60 |
| Supramarginal gyrus | L | | -57 | -21 | 15 | 3.57 |

[1] Peaks (in MNI space) listed are statistically significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent = 22 voxels, 3 × 3 x 3 mm voxels, * indicates $p < 0.05$ FWE corrected at cluster level); L, left; R, right.