NeuroImage 201 (2019) 116016

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Development and body mass inversely affect children's brain activation in dorsolateral prefrontal cortex during food choice

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ARTICLE INFO

Keywords:
Development
Overweight
Decision making
fMRI
Food choice

ABSTRACT

Childhood obesity is a rising problem caused in part by unhealthy food choices. Food choices are based on a neural value signal encoded in the ventromedial prefrontal cortex, and self-control involves modulation of this signal by the dorsolateral prefrontal cortex (dlPFC). We determined the effects of development, body mass (BMI Cole score) and body mass history on the neural correlates of healthy food choice in children. 141 children (aged 10-17y) from Germany, Hungary and Sweden were scanned with fMRI while performing a food choice task. Afterwards health and taste ratings of the foods were collected. In the food choice task children were asked to consider the healthiness or tastiness of the food or to choose naturally. Overall, children made healthier choices when asked to consider healthiness. However, children who had a higher weight gain per year chose less healthy foods when considering healthiness but not when choosing naturally. Pubertal development stage correlated positively while current body mass correlated negatively with dlPFC activation when accepting foods. Pubertal development negatively and current body mass positively influenced the effect of considering healthiness on activation of brain areas involved in salience and motivation. In conclusion, children in earlier stages of pubertal development and children with a higher body weight exhibited less activation in the dlPFC, which has been implicated in self-control during food choice. Furthermore, pubertal development and body mass influenced neural responses to a health cue in areas involved in salience and motivation. Thus, these findings suggest that children in earlier stages of pubertal development, children with a higher body mass gain and children with overweight may possibly be less susceptible to healthy eating interventions that rely on self-control or that highlight health aspects of food.

1. Introduction

Childhood obesity is a growing problem (Wang and Lobstein, 2006). In addition to a lack of physical activity, overconsumption is an important contributor to positive energy balance and thus weight gain (Blundell and Cooling, 2000). Energy intake is determined by choices about when, how much and what to eat. To determine which factors may contribute to the development or maintenance of childhood obesity, we need to understand how these food choices come about in children, how this may change over development and how this is related to weight

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https://doi.org/10.1016/j.neuroimage.2019.116016
Received 22 November 2018; Received in revised form 17 June 2019; Accepted 11 July 2019
Available online 13 July 2019

status.

Food choices are made in the brain, which integrates a multitude of neural and hormonal signals reflecting internal state and environmental factors (Smeets et al., 2012). In the decision making process different aspects of the choice options are combined into a single neural value. This value reflects aspects relevant to the individual, such as taste, healthiness and the cost or effort required to obtain that food (Rangel, 2013). This assignment of value occurs in the ventromedial prefrontal cortex (vmPFC) (Hare et al., 2009, 2011; Litt et al., 2011). Valuation activation in the vmPFC is strongly correlated with the tastiness of foods (Hare et al., 2009, 2011). However, when dieters successfully make healthy choices, activity in the vmPFC is correlated with the healthiness of the foods, and vmPFC activity is modulated by the dorsolateral prefrontal cortex (dlPFC) (Hare et al., 2009). Interestingly, when people who are not on a diet are asked to consider the healthiness of foods during their choice, their brain response and behavior mimics that of successful dieters: their vmPFC activation is correlated with the healthiness of the food, there is more connectivity with the dlPFC, and they make healthier choices (Hare et al., 2011). This suggests that in adults, guiding attention towards health aspects facilitates healthier food choices by triggering dlPFC activation and enhancing connectivity between the dlPFC and vmPFC (Hare et al., 2011).

The neural mechanisms underlying food choice may be different in children because their prefrontal cortex (PFC) is not yet fully matured. Areas in the PFC, such as the dlPFC, mediate the capacity to voluntarily inhibit desire for a short-term reward in favor of a (larger) long-term reward (Watanabe et al., 2002) and are thus important for self-control. To our knowledge, there are only three studies on the neural correlates of healthy food choice in children. These studies found that in children tastiness of foods greatly contributed to the decisions while healthiness did not (Bruce et al., 2016; Lim et al., 2016; van Meer et al., 2017). In an earlier study we compared food choices between children (10–12 years) and adults and asked them to consider the healthiness or tastiness of foods or to choose naturally (van Meer et al., 2017). Overall, children chose fewer healthy foods than adults and had weaker dlPFC activation during choice. Furthermore, considering healthiness promoted healthier choices in both children and adults, but was accompanied by an opposing pattern of brain activation in the medial PFC. However, it remains unclear how these processes change as children develop and how this is related to their weight status.

The relationship between body mass and the neural correlates of healthy food choice in children has not yet been examined to our knowledge. In addition to current body mass, body mass history may affect the neural correlates of food choice as well. Although a growing number of studies, mostly in adults, found that brain responses to food cues can predict weight change (e.g. (Winter et al., 2017; Yokum et al., 2014; Yokum et al., 2011)), the effect of weight change (loss or gain) on brain responses to food has received less attention. After weight loss, adults had reduced precentral gyrus activation and increased inferior frontal gyrus (dlPFC) activation during food compared with non-food viewing (Rosenbaum et al., 2008). Young adults with overweight/-obesity who gained weight showed lower caudate activation in response to milkshake intake (Stice et al., 2010), while adolescents who gained body fat had a greater increase in putamen, precuneus and rolandic operculum activation in response to a milkshake cue (Stice and Yokum, 2016). Thus, weight loss may lead to stronger activation in self-control and weaker activation in areas involved in reward processing while weight gain may lead to stronger activation during anticipation in these latter areas.

We determined the effect of pubertal development, current body mass, and body mass history on the neural correlates of food choice in children, and examined whether these factors influence the effect of attending to the healthiness of food. We expected younger children, children with a higher body mass and children who gained weight to make fewer healthy choices and be less affected by considering the healthiness on their choice behavior. In line with this, we expected children further in pubertal development to have stronger activation in the dlPFC during food choice. Additionally, we expected children with a higher current body mass and children who gained weight to have less activation in the dlPFC and more activation in areas involved in reward processing, such as the striatum and the orbitofrontal cortex.

2. Methods

2.1. Participants

The children included were part of the IDEFICS cohort which was followed-up during the I.Family study. In the IDEFICS (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) baseline survey in 2007/2008, a population-based sample of 16,228 children aged 2–9.9 years from eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, Sweden) was examined. Follow-up examinations were conducted two years (IDEFICS) and six years (I.Family study; 7105 children) later; the study design has been described in detail elsewhere (Ahrens et al., 2016). A subsample of 192 out of these 7105 children in I.Family centers in Hungary, Germany and Sweden were scanned with fMRI. Care was taken to prioritize the inclusion of overweight children and children who had gained weight to ensure enough variation in the sample. For the current analyses, data of 141 children was available.

Children were included if they matched MRI inclusion criteria. The exclusion criteria were being left-handed, having an eating disorder, having a food allergy, following a diet (whether medically prescribed or to lose weight), or having a history of surgical or medical events (such as gastro-intestinal disorders) that may affect the study outcome. All children provided assent and their parents provided written informed consent 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. The data of 51 children could not be used for analysis, because of excess movement ($n = 11$), a missing or incomplete log file of the choice task ($n = 22$), missing food picture ratings ($n = 4$), missing baseline weight and height ($n = 4$) and lack of variety in the choices in the food choice task ($n = 10$; see section 'Food choice fMRI task'). This leaves a final sample of 141 children (see Table 1 for demographics). There were no differences in Tanner stage, BMI Cole score and BMI Cole score change between the children whose data was not used and the children whose data was included (Tanner stage: $t(188) = -1.2$, $p = 0.24$; BMI Cole score: $t(186) = -1.4$, $p = 0.16$; BMI Cole score change: $t(184) = -1.2$, $p = 0.24$).

2.2. Procedure

Prior to the scan, children were familiarized with the procedure and the tasks through movie clips and a practice version of the task. Participants were requested to refrain from eating and drinking (except water) for 2 h prior to the scan session. Participants' height and weight were measured and they completed visual analogue scales (VAS) recording their hunger and fullness. Subsequently, they performed a food choice task while being scanned. Afterwards, participants rated the healthiness and tastiness of the foods from the food choice task ($n = 150$) on a five point scale in a rating task on the computer.

2.3. Variables

2.3.1. Pubertal development

Maturation stages according to Tanner were self-reported by the children with pictograms (Table 1). Since pubertal development is thought to be to be more closely related to brain development than age alone (Blakemore et al., 2010; Goddings et al., 2019; Herting and Sowell, 2017), this variable was considered the most informative.

Table 1
Demographic variables per center and across all centers.

	Bremen ($n = 35$, 18F)			Gothenburg ($n = 32$, 19F)			Pecs ($n = 74$, 43F)			Total ($n = 141$, 80F)		
	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD
Age	13.5	11–16	1.42	12.8	10–16	1.88	13.4	10–17	1.90	13.4	10–17	1.80
BMI Cole score	0.54	−0.99–2.87	0.93	0.29	−0.99–2.87	0.93	0.53	−2.83–3.03	1.14	0.48	−2.83–3.03	1.04
BMI Cole score change[a]	0.05	−0.17–0.27	0.09	0.04	−0.14–0.24	0.08	0.06	−0.21–0.39	0.14	0.05	−0.21–0.39	0.12
Tanner stage	2.57	1–3	0.50	2.28	2–3	0.73	2.42	1–3	0.55	2.43	1–3	0.59
Time since last meal	3.6	0.4–7.5	1.9	3.2	0.3–14.5	2.2	3.9	1.45–19	2.9	3.7	0.3–19	2.5
Hunger rating[b]	10.7	3–20	5.3	7.3	0–20	5.5	9.1	0–20	5.1	9.1	0–20	5.3
Fullness rating[c]	6.9	0–17	5.3	13.4	5–20	4.3	6.0	0–16	4.6	8.0	0–20	5.6

[a] Difference in BMI Cole score between the scan day and the first measurement in the IDEFICS study divided by the time between measurements in years.
[b] Hunger and Fullness ratings were recorded on visual analogue scales and converted to a score between 0 and 20.
[c] There was a difference between centers in Fullness rating ($F(2,139) = 30.3$, $p < 0.001$). There were no statistically significant differences between centers for the other variables.

2.3.2. Current body mass

BMI Cole score was determined (Cole and Lobstein, 2012) from the BMI calculated using the height and weight measurements. The BMI Cole score is an SD score that takes in to account the specific skewness, mean and variation of BMI centile curves that change smoothly with and differ per sex. The norms of the 2012 Independent Task Obesity Task Force norms were used (Cole and Lobstein, 2012). The World Health Organization uses the following cut-offs in children over 5 y: BMI Cole score −2 for thinness, +1 for overweight and +2 for obesity.

2.3.3. Body mass change

To assess weight change the difference in BMI Cole score between the scan day and the first measurement in the IDEFICS study was calculated and divided by the time between measurements in years. The mean time between measurements was 7.24 years (SD 0.89). If a child has a positive BMI Cole score change this indicates that they gained weight relative to their place on the BMI curve for their age and sex in the first measurement and if they have a negative BMI Cole score change this indicates they relatively lost weight.

2.4. Food choice fMRI task

This experiment used a food choice task adapted from Hare et al. (2011), see Fig. 1 for a schematic representation. To facilitate the comparison of results with the results of our previous study, the task, data acquisition and data analysis have been kept the same as in van Meer et al. (2017), where possible. In our 2017 study the comparison between children and adults was the main outcome, while in this study, the substantially larger sample size allowed for the examination of the critical effects of body mass, body mass change and pubertal stage in children. A single-item food choice task was used in which food pictures were presented for 2 s followed by a 2 s period in which children could select a response. Children were asked to indicate with 'yes' or 'no' whether they wanted to eat a food after the scan by pressing a button with their left or right thumb respectively as in van der Laan et al. (2014) and van Meer et al. (2017). The task consisted of 150 trials, one of which was selected, and if the child said 'yes' in this trial they received this food product after the scan, if they said no they did not receive a food product. A variable inter-trial interval between (ITI) 1.4–4.0 s separated the trials. Optseq2 was used to optimize the ITI, sequence of trials and to counterbalance trials while keeping the block duration constant (https://surfer.nmr.mgh.harvard.edu/optseq/) (Dale, 1999). The task consisted of three different attention conditions. The children were asked to consider the healthiness of the food in the health condition, the taste of the food in the taste condition or to choose naturally in the natural condition. Before the task the children were instructed that 'choose naturally' here meant: choose as if there are no specific instructions, simply indicate whether or not you would like to eat the food after the task or not. To ensure that children's choices were still based on preference, the instructions emphasized that, regardless of the condition, one of the foods will be selected for their snack after the scan, so they should always select the foods they really want to eat. A 5 s instruction screen appeared at the beginning of each condition and there were 10 trials per condition. The task consisted of 5 blocks per condition, 150 trials in total. There was no repetition of food images and the order of conditions was random for each participant. The food images used were selected from the Full4-Health Image Collection (Charbonnier et al., 2016) and piloted in children in each of the countries to ensure familiarity with the foods. To remind children about which condition they were in, a colored dot was shown. The dot was dark blue for the natural condition, green for the health condition and orange for the taste condition. Children who had too little variation in their responses, i.e. accepted less than 10% of the items or rejected less than 10% of the items, were excluded from the analyses (n = 10). Children viewed the stimuli via a mirror on the head coil or with goggles with use of the PRESENTATION software (Neurobehavioral Systems Inc., Albany, CA).

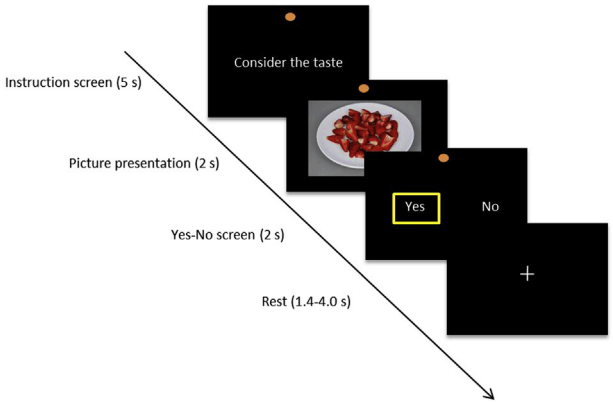

Fig. 1. Trial structure of the food choice task.

2.5. MRI data acquisition

MRI scanning was performed in the three centers on 3 T MRI scanners (Germany: Siemens Skyra; Hungary: Siemens Trio, Siemens AG, Erlangen, Germany; Sweden: GE Discovery MR750w, GE Healthcare Systems, Milwaukee, USA), using a 32-channel head coil (Germany, Sweden) or a 12-channel head coil (Hungary). A T_1-weighted structural image was acquired at a resolution of 1 × 1 × 1 mm with 176 sagittal slices and a field of view of 256 × 256 (Germany: repetition time (TR) = 1900 ms, echo time (TE) = 2.07 ms, flip angle 9°; Hungary: TR = 2530 ms, TE = 3.37 ms, flip angle 7°; Sweden: TR = 6.928 ms, TE = 2.53 ms, flip angle 7°). The functional scan was a T_2*-weighted gradient echo 2D-echo planar imaging sequence (TR/TE = 2000/30 ms, flip angle = 76°, 36 axial slices, voxel size = 3 × 3 × 3 mm, at all sites).

2.6. Behavioral data analysis

Four mixed-effects logistic regression models were estimated to analyze the behavioral component of the food choice task. In each model, choice outcome (yes or no) was the dependent variable and the predictors were regressors for health rating, taste rating, the interaction of health condition and health rating (HR*HC), the interaction of health condition and taste rating (TR*HC), the interaction of taste condition and health rating (HR*TC), the interaction of taste condition and taste rating (TR*TC), and dummies for taste and health condition. Tanner stage, BMI Cole score, BMI Cole score change and two dummies for center were added as covariates. The first model examined task effects controlled for the covariates. The other three models examined interactions between a covariate of interest (Tanner stage, BMI Cole score or BMI Cole score change) and the task-related predictors while controlling for the other covariates. To correct for the fact that four models were tested, Bonferroni correction was used so only results that had a *p*-value below the critical *p*-value of 0.0125 (0.5/4) were considered significant.

2.7. fMRI data preprocessing

SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) run with MATLAB R2015b (The Mathworks Inc, Natick, MA) was used for data preprocessing and analysis. First, slice time correction was applied on the data, using the middle slice as a reference. Second, the functional images were realigned to the first scan. After grey and white matter segmentation, a study-specific anatomical template was created using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) (Ashburner, 2007). After performing co-registration, DARTEL was used to normalize the template and the functional scans to MNI space. Afterwards, the data was smoothed, using a 6 mm full width at half maximum isotropic Gaussian kernel. Finally, anomalously noisy volumes that moved more than 1 mm/TR were repaired using the Volume Artefact tool from ArtRepair (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). This resulted in the exclusion of 11 children because too many volumes (>25%) had to be repaired.

2.8. Subject level analyses

All data were high-pass filtered with a cutoff of 128 s. Statistical maps for each participant were generated by fitting a boxcar function to the time series, convolved with the canonical hemodynamic response function. The following first level model was estimated: all decision events (2 s) were modeled with yes and no as a parametric modulator, a regressor for health condition (74 s, from after the instruction screen until the end of the block) and a regressor for taste condition (74 s, from after the instruction screen until the end of the block). The instruction screen announcing a new condition (5 s), the yes-no screen (2 s) and realignment parameters were modeled as regressors of no interest. Parametric modulators were orthogonalized. The following contrasts were calculated: 1) decision events modulated by yes vs. no, 2) health condition effect, and 3) taste condition effect. Note that, given the specification of the model, contrasts 2 and 3 measure the change in average activity (independent of choice outcome) with respect to the natural control condition.

A second subject-level model estimated the effects of healthiness and tastiness ratings and their interactions with the conditions and is described in Supplement 1.

2.9. Group level analyses

One-sample t-tests were used to examine effects for the contrasts calculated in the subject level analyses. Tanner stage, BMI Cole score and BMI Cole score change were added in the same model as covariates. Two dummy variables for center (encoding for the three levels of center, Gothenburg, Bremen and Pecs) were added as covariates of no interest to control for between-site differences.

We hypothesized to find effects in areas implicated in the appetitive brain network (Dagher, 2012): medial and lateral PFC, anterior cingulate cortex, insula, striatum, hippocampus and amygdala. We did not include the solitary nucleus/ventral tegmental area and the hypothalamus, since these are too small to assess reliably given our resolution. To test for effects in these a priori regions of interest (ROIs) a single binary mask (voxel count: 10954) containing all the ROIs bilaterally was created using the Automated Anatomical Labeling (AAL) atlas as implemented in the Wake Forest University (WFU) Pickatlas toolbox (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). For the sake of completeness and to enable future meta-analysis, we report whole brain results as well.

A cluster level threshold of $p < 0.05$ corrected for multiple comparisons across the mask volume was derived using Monte Carlo simulations (10,000 iterations) of random noise distribution across the whole brain an in the ROI mask using the 3dClustSim tool in AFNI version 16.2.07(Cox, 1996; Forman et al., 1995). Here, an individual voxel probability threshold is combined with a minimum cluster size to estimate the probability of a false positive. The 3DFWHMx tool in AFNI was used to estimate the smoothness values of the noise using the Auto-Correlation Function (ACF) option. The resulting 2-sided threshold was $p < 0.001$ with a cluster extent $k \geq 28$ for the ROI mask and $p < 0.001$ with a cluster extent $k \geq 57$ for the whole brain.

3. Results

3.1. Behavioral results

Four mixed-effects logistic regression models were estimated with choice outcome.

3.1.1. Main effects

To see which factors predicted choice outcome we assessed the effects of health and taste ratings and the different conditions controlled for Tanner stage, BMI Cole score and BMI Cole score change (Model 1; see Fig. S1a in Supplement 1). There were positive effects of health ($b = 0.13$, $p < .001$) and taste rating ($b = 1.46$, $p < .001$) in the natural condition. There were significant interaction effects between health rating and health condition ($b = 0.30$, $p < .001$), taste rating and health condition ($b = -0.38$, $p < .001$), health rating and taste condition ($b = -0.11$, $p = 0.002$) and taste rating and taste condition ($b = 0.14$, $p < .001$). This means that overall children adhered to the condition instructions; when asked to consider the healthiness of the foods they chose more based on healthiness and less on taste, when asked to consider the taste of the foods they chose more based on taste and less based on healthiness, and when choosing naturally they chose mostly based on taste but healthiness predicted choice as well.

Since our main interest was the effects of pubertal development, body mass and body mass history, the next three models examined interactions between a covariate of interest (Tanner stage, BMI Cole score or BMI Cole score change) and the task-related predictors while controlling for the other covariates.

3.1.2. Pubertal development

There was a main effect of Tanner stage on choice outcome (Model 2; Fig. S1b; $b = -1.0$, $p < 0.001$), meaning that more physically mature children accepted foods less often. There were interactions between Tanner stage and taste rating in the natural condition ($b = 0.22$, $p < 0.001$) and a trend for an interaction between Tanner stage and health rating in the health condition ($b = 0.11$, $p = 0.057$). This indicates that more physically mature children may be more responsive to health features during the health condition than less physically mature children. Additionally, taste was a stronger predictor of acceptance in the natural condition for children further in pubertal development, which was an unexpected finding.

3.1.3. Current body mass

There was no main effect of BMI Cole score on choice outcome, which means that children with a higher current body mass did not accept or reject more foods (Model 3; Fig. S1c). However, there was an interaction effect between BMI Cole score and taste rating in the natural condition ($b = -0.09, p < 0.001$). This indicates that the taste rating of the accepted food was lower for children with a higher BMI Cole score, which is again not something that we had hypothesized.

3.1.4. Body mass history

There was a trend towards a main effect of BMI Cole score change on choice outcome (Model 4; Fig. S1d; $b = 2.83, p = 0.045$) which indicates that children with a higher positive weight change accepted foods more often than children who gained less weight or lost weight. There was an interaction effect between BMI Cole score change and taste rating in the natural condition ($b = -1.12, p < 0.001$) and BMI Cole score change and health rating in the health condition ($b = -0.64, p < .001$) and a trend towards taste rating in the health condition ($b = 0.74, p = 0.036$). This indicates that in the natural condition the taste rating of the accepted food was lower for children with a higher positive weight change. This is in line with the findings regarding pubertal development and current body weight. Furthermore, children who gained more weight were less responsive to health features during health condition and more responsive to taste features during health condition than those who gained less weight or lost weight.

On average the taste and health ratings of the foods were weakly positively correlated (mean correlation coefficient across participants $r = 0.15$ (SD 0.33), this value was significantly greater than 0, $t(140) = 5.24$, $p < 0.001$). This correlation per participant was not correlated with any of the variables of interest (BMI Cole score, BMI Cole score change or Tanner stage). BMI Cole score was correlated with BMI Cole score change ($r = 0.40$, $p < 0.001$) and Tanner stage ($r = 0.20$, $p = 0.017$). Tanner stage was not significantly correlated with BMI Cole score change ($r = -0.09$, $p = 0.27$).

It is possible that factual knowledge of the actual healthiness of foods differs between children. To examine this, we assessed the 'true' healthiness of each of the foods in the pictures by determining the Nutritional Rich Food (NRF) score (Drewnowski, 2010). The NRF produces a single score per food based on the sum of the percentage of daily values for 9 nutrients to encourage (protein, fiber, vitamin A, vitamin C, vitamin E, calcium, iron, magnesium, and potassium) minus the sum of the percentage of maximum recommended values for 3 nutrients to limit (saturated fat, total sugar, and sodium), with all daily values calculated per 100 kcal and capped at 100%. On average there was a moderate correlation between the NRF score per food and the health rating per food given by the children (mean $r = 0.39$, SD = 0.08; $t(140) = 60.0$, $p < 0.001$). The NRF-health rating correlation per child did not correlate with BMI Cole score ($r = -0.01$, $p = 0.95$) or BMI Cole score change ($r = -0.09, p = 0.30$). It did correlate weakly with Tanner stage ($r = 0.26$, $p = 0.002$). This indicates that the health ratings of more developmentally mature children are more accurate. Since for this study we are interested in brain responses during what children themselves consider to be healthy choices, the subjective health ratings are used.

A mixed-effects regression model was estimated with reaction time as dependent variable and taste rating and health rating as regressors. The interactions with Tanner stage, BMI Cole score and BMI Cole score change were modeled as well (Supplement 1). Since the reaction times were not related to any of the variables of interest and their interpretation is complicated by the task design we have not added them to the fMRI model.

3.2. Imaging results

3.2.1. Main effects

3.2.1.1. Choice outcome. To examine the effect of choice outcome (yes greater than no) and the effects of health condition and taste condition we estimated a subject level model with a regressor for choice event, a parametric modulator for yes/no, and a regressor for health condition and taste condition. We performed a one-sample *t*-test with Tanner stage, BMI Cole score, BMI Cole score change and center as covariates. The main effects of this test showed that there was stronger activation in response to yes than no in the right putamen/amygdala, anterior cingulate cortex/medial superior frontal gyrus (vmPFC) right olfactory bulb and left middle frontal gyrus (dlPFC) (Table 2). The whole brain analysis additionally showed significant clusters in the right precentral gyrus, bilateral middle occipital gyrus, right calcarine sulcus, left supramarginal gyrus and left caudate nucleus.

3.2.1.2. Effect of health condition. To examine the effect of considering healthiness on the neural response to food choice we performed a one-sample *t*-test on the effect of health condition on choice with Tanner stage, BMI Cole score, BMI Cole score change and center as covariates. When considering the healthiness of the food during choice, children had more activation in left superior frontal gyrus (dLPFC) compared with the natural choice condition (Table 3). The whole brain analysis additionally showed significant clusters in the medial lingual gyrus/calcarine sulcus/superior occipital gyrus, and the left supplementary motor area.

3.2.1.3. Effect of taste condition. We performed a one-sample *t*-test on the effect of taste condition on the neural response to food choice, again with

Table 2
Brain regions with significant activation in the yes vs. no contrast of the food choice task across all attention conditions.

Brain region[a]	Side	Cluster size	x	y	z	Z-score[b]
ROIs						
Putamen	R	499	30	−12	0	Inf
Amygdala	R		27	−3	−9	Inf
Insula	R		39	−15	15	Inf
Anterior cingulum	L	379	−12	39	0	6.90
Medial orbital superior frontal gyrus	R/L		0	45	−9	6.74
Medial orbital superior frontal gyrus	R		9	51	−9	6.58
Olfactory	R	30	3	9	−6	6.16
Olfactory	R		6	18	−3	5.05
Middle frontal gyrus	L	105	−27	27	42	4.59
Middle frontal gyrus	L		−21	12	51	4.01
Whole brain						
Precentral gyrus	R	4142	36	−21	54	Inf
Thalamus	R		15	−21	3	Inf
Rolandic operculum	R		42	−21	18	Inf
Middle occipital gyrus	L	599	−39	−78	30	Inf
Middle occipital gyrus	L		−24	−78	18	7.05
Middle occipital gyrus	L		−51	−75	18	6.94
Calcarine sulcus	R	152	12	−90	6	7.44
Medial orbital superior frontal gyrus	L	768	−12	39	−6	6.90
Medial orbital superior frontal gyrus	R/L		0	45	−9	6.74
Olfactory	R		3	12	−6	6.58
Middle occipital gyrus	R	360	42	−69	27	6.68
Middle temporal gyrus	R		57	−51	−3	6.18
Middle temporal gyrus	R		51	−54	3	5.77
Supramarginal gyrus	L	109	−63	−39	39	5.92
Supramarginal gyrus	L		−66	−24	30	3.44
Caudate nucleus	L	131	−21	−18	30	5.66
Caudate nucleus	L		−18	−6	24	3.44
Middle frontal gyrus	L	106	−27	27	39	4.59
Middle frontal gyrus	L		−21	12	51	4.01

[a] Peaks listed are significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent = 57 voxels, 3 × 3x3 mm voxels) and/or within an a priori set of regions of interest (individual voxel threshold = $p < 0.001$, cluster extent = 28 voxels, 3 × 3x3 mm voxels). L, Left; R, right; ROIs, regions of interest.

[b] Infinite Z score (Inf) is due to the very small P value.

Table 3
Brain regions with significant activation in health condition vs. natural condition contrast of the food choice task.

Brain region[a]	Side	Cluster size	x	y	z	Z-score
ROIs						
Superior frontal gyrus (dlPFC)	L	60	−12	33	54	5.44
Superior frontal gyrus (dlPFC)	L		−12	15	57	4.70
Whole brain						
Lingual gyrus	R	284	9	−87	−6	7.35
Calcarine sulcus	L		−6	−87	−9	6.93
sSuperior occipital gyrus	L		−9	−96	6	5.67
Supplementary motor area	L	150	−6	12	51	5.44
Superior frontal gyrus (dlPFC)	L		−12	33	54	5.44
Superior medial frontal gyrus	L		−6	30	36	3.53

[a] Peaks listed are significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent = 57 voxels, 3 × 3x3 mm voxels) and/or within an a priori set of regions of interest (individual voxel threshold = $p < 0.001$, cluster extent = 28 voxels, 3 × 3x3 mm voxels). L, Left; R, right; ROIs, regions of interest.

Tanner stage, BMI Cole score, BMI Cole score change and center as covariates. There were no overall effects of taste condition, which suggest that when choosing naturally children mainly consider the taste of foods.

3.2.2. Pubertal development

3.2.2.1. Choice outcome. Tanner stage correlated positively with brain activation in the contrast of yes greater than no in the left triangular part of the inferior frontal gyrus (dlPFC; Table 4; Fig. 2). To check whether the effect was driven by the smaller number of children in stage 1, we have repeated the analysis comparing the children in stage 2 and stage 3. The cluster in the dlPFC was remained significantly more activated in children in stage 3 than in children in stage 2 ($Z = 4.02$, cluster extent = 32, $p < 0.001$). Thus, children in earlier stages of pubertal development had weaker activation in the left dlPFC.

3.2.2.2. Effect of health condition. The whole brain analysis revealed a negative correlation between the effect of health condition and Tanner stage in the middle temporal gyrus in this model. This indicates that children who were earlier in pubertal development had stronger activation in the middle temporal gyrus.

3.2.2.3. Effect of taste condition. There were no correlations between the effect of taste condition and Tanner stage in this model.

3.2.3. Current body mass

3.2.3.1. Choice outcome. In this model BMI Cole score was negatively correlated with yes greater than no activation in the right insula and the left middle frontal gyrus (dlPFC; Table 5). In the whole brain analysis a cluster in the superior temporal gyrus was found. Thus, children with a higher current body mass had weaker activation in the dlPFC.

3.2.3.2. Effect of health condition. There was a positive correlation between the effect of health condition and BMI Cole score in the cerebellum in the whole brain analysis. Thus, children with a higher current body mass have greater activation in the cerebellum.

3.2.3.3. Effect of taste condition. There was a negative correlation between the effect of taste condition and BMI Cole score in the right middle frontal gyrus (dlPFC). Thus, children with a higher current body mass had weaker dlPFC activation during the taste compared to the natural condition.

3.2.4. Body mass history

3.2.4.1. Choice outcome. BMI Cole score change was positively correlated with the activation in response to yes versus no in the bilateral calcarine sulcus/lingual gyrus (Fig. 3; Table 6) in the whole brain analysis. Thus, children with a higher positive weight change had stronger activation in areas involved in visual processing.

3.2.4.2. Effect of health & taste condition. There were no correlations between the effect of health or taste condition and BMI Cole score change in this model.

A second model was estimated to examine the associations between Tanner stage, BMI Cole score, BMI Cole score change and the effect of taste and health ratings on brain activation in the different conditions (see Supplement 1 for the model specification and results).

To ensure that the effects of the variables of interest were independent of interindividual variation in motion we have calculated the average Framewise Displacement (FD) per person using the method of Power et al. (2012). The mean FD was 0.25 mm (SD 0.19). There were no significant correlations between FD and BMI Cole score, BMI Cole score change or Tanner stage. We have estimated the fMRI model with the average FD per person as a covariate. The results of this model remain mostly the same; two clusters no longer reach our threshold for significance (negative correlation between BMI Cole score and activation in the left middle frontal gyrus in the yes vs. no contrast, negative correlation between Tanner score and activation in the right temporal gyrus in the health vs. natural condition). We additionally estimated an fMRI model with sex as a covariate to correct for gender differences. This changed none of the results. There were no differences between males and females in BMI Cole score, BMI Cole score change or Tanner stage.

Table 4
Brain regions with significant correlation with Tanner stage during the food choice task.

Brain region[a]	Side	Cluster size	x	y	z	Z-score
Yes vs. no						
Positive correlation with Tanner stage						
ROIs						
Inferior frontal gyrus triangular part	L	30	−36	9	21	4.18
Whole brain						
Inferior frontal gyrus triangular part	L	77	−33	9	21	4.84
Effect of health condition						
Negative correlation with Tanner stage						
Whole brain						
Middle temporal gyrus	R	60	45	−54	3	3.90
Middle temporal gyrus	R		51	−57	15	3.59
Middle temporal gyrus	R		54	−60	6	3.39

[a] Peaks listed are significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent = 57 voxels, 3 × 3x3 mm voxels) and/or within an a priori set of regions of interest (individual voxel threshold = $p < 0.001$, cluster extent = 28 voxels, 3 × 3x3 mm voxels). L, Left; R, right; ROIs, regions of interest.

4. Discussion

We determined the effect of pubertal development, current body mass, and body mass history on the neural correlates of food choice in children, and whether these factors influence the effect of attending to the healthiness of food. Our findings suggest that younger children and children who have or who are getting overweight have less activation in cognitive control areas during food choice and are less responsive to attention manipulations intended to promote healthier choices by

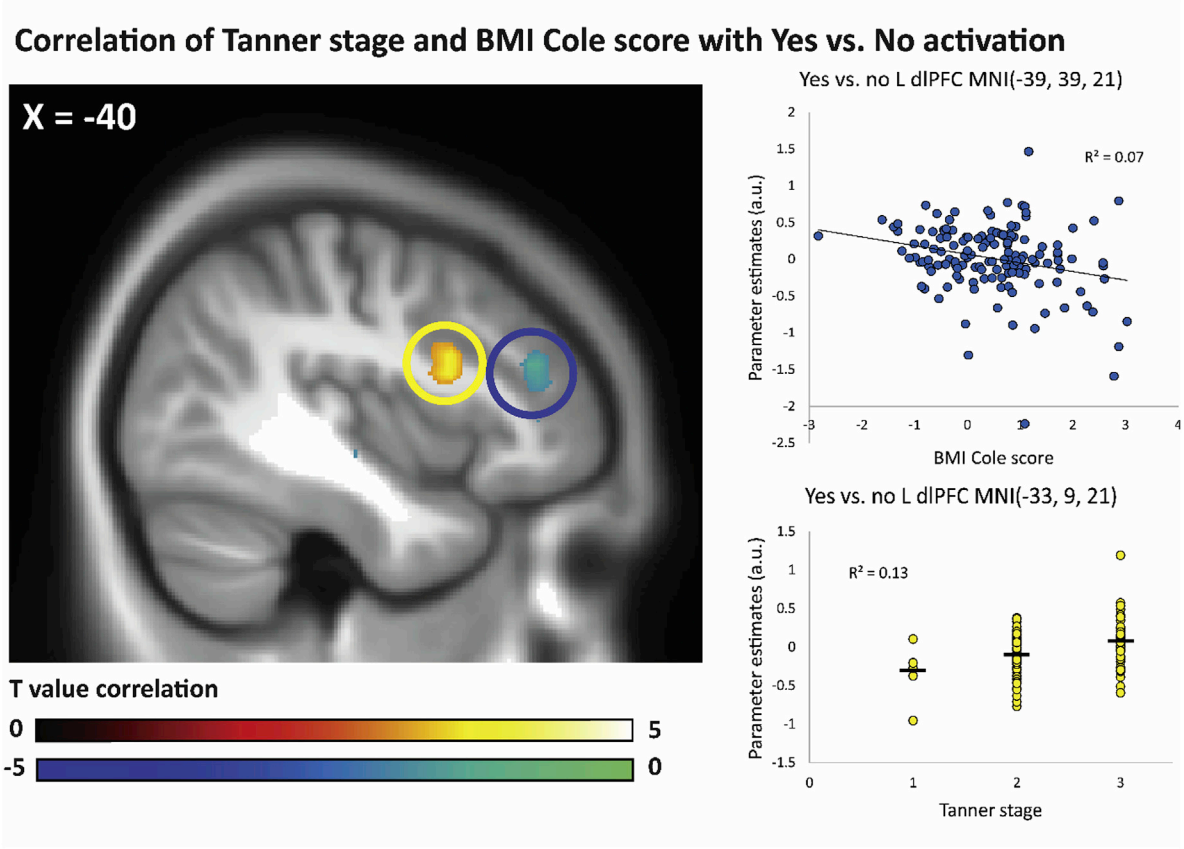

Fig. 2. Correlation of Tanner stage and BMI Cole score with modulation of choice activation by yes vs. no independent of condition. Blue circle denotes negative correlation with BMI Cole score and yellow circle denotes positive correlation with Tanner stage. Peaks listed are significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent threshold > 57 voxels, 3 × 3x3 mm voxels) and within an a priori set of regions of interest (individual voxel threshold $p < 0.001$, cluster extent > 28 voxels, 3 × 3x3 mm voxels).

emphasizing health aspects.

Our behavioral analyses showed that children in an earlier pubertal stage accepted more foods during the food choice task. The health ratings of these children were less accurate than those of children in a later pubertal stage. Furthermore, children who relatively gained weight chose less healthy foods when considering the healthiness of the foods. In children in an earlier pubertal stage, children with higher current body mass and with greater weight gain, taste ratings were less predictive of choice in the natural condition. This suggests that children who are developmentally younger or have a higher relative weight gain may discriminate less on taste; their taste criterion for saying yes may have been lower. This sheds a different light on our findings regarding the smaller effect of the health cue in these children as well, because this could be caused by a less discriminative food choice style overall in children with higher weight gain and/or in an earlier pubertal stage.

We then examined the effect of pubertal development on the neural responses to food choice and found that children in a later pubertal stage had stronger dlPFC activation in response to yes versus no during food choice. Having stronger activation when accepting than rejecting foods can be viewed as an effect of approach towards food, in this case in an area involved in cognitive control. This is in line with the differences in food choice activation observed between children and adults in our previous study (van Meer et al., 2017) and previous work that found an increase in dlPFC activation and better performance during a task with choices involving a trade-off between immediate and delayed rewards and stronger vmPFC-dlPFC activation as a function of age (Steinbeis et al., 2016).

We also examined the relationship between brain responses and current body mass (BMI Cole score). Children with a current higher body mass had weaker activation in an area in the left dlPFC when saying yes to foods. This is in line with previous research in which children with a higher BMI had lower dlPFC activation in response to watching unhealthy food pictures (van Meer et al., 2016) and children with a higher BMI had lower dlPFC activation in response to palatable foods in a go/no-go task (Batterink et al., 2010), although the opposite has been found as well, see (Bruce et al., 2010; Davids et al., 2010; Stice et al., 2008). In a recent study, excess-weight children had higher dlPFC activation than normal-weight children when making a choice between an appetizing and plain food compared with baseline (Moreno-Padilla et al., 2018). This incongruence in findings between studies suggests that the dlPFC may respond differently during food choice in overweight children than normal-weight children, but that the direction of the effect may be dependent on the specific task and contrast examined. Specifically, their finding could reflect a difference in baseline activity between the BMI groups. In conclusion, our results suggest that children with a higher current body mass engage this area involved in cognitive control less when accepting foods during choice. Children with a higher current body mass had a smaller change in dlPFC activity due to the taste condition as well. This could indicate that for children with a lower current body mass, considering the taste of the foods increases their dlPFC activation more than in children with a higher current body mass.

Finally, we examined the correlation between body mass history and neural responses to food choice. Children with greater weight gain had stronger activation in the bilateral calcarine sulcus/lingual gyrus when accepting foods, independent of attention condition. This could be due to a higher saliency of food for children who gained weight. This supports

Table 5
Brain regions with significant correlation with BMI Cole score during the food choice task.

Brain region[a]	Side	Cluster size	x	y	z	Z-score
Yes vs. no						
Negative correlation with BMI Cole score						
ROIs						
Insula	R	64	45	6	−3	4.22
Insula	R		48	12	−9	4.07
Middle frontal gyrus	L	28	−39	39	21	3.66
Inferior frontal gyrus triangular part	L		−48	36	27	3.44
Whole brain						
Superior temporal gyrus	R	82	48	−15	3	4.96
Insula	R	100	42	6	−3	4.45
Insula	R		48	12	−9	4.07
Superior temporal pole	R		54	9	−3	4.00
Effect of health condition						
Positive correlation with BMI Cole score						
Whole brain						
Cerebellum	R	144	9	−45	−15	4.60
Vermis	L		−3	−51	−9	4.33
Cerebellum	R		9	−66	−12	3.52
Effect of taste condition						
Negative correlation with BMI Cole score						
ROIs						
Middle frontal gyrus	R	41	42	48	15	3.98
Middle frontal gyrus	R		36	45	27	3.70

[a] Peaks listed are significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent = 57 voxels, 3 × 3x3 mm voxels) and/or within an a priori set of regions of interest (individual voxel threshold = $p < 0.001$, cluster extent = 28 voxels, 3 × 3x3 mm voxels). L, Left; R, right; ROIs, regions of interest.

the previous finding that adolescents who gain body fat have greater activation in reward related area (Stice and Yokum, 2016) during food anticipation. Additionally, a correlation between lingual gyrus activation and BMI was found for adolescents when looking at food compared with non-food commercials (Yokum et al., 2014). Taken together, foods may be more salient to children who have gained more weight, and this may be accompanied with a less discriminative choice style. This could mean that for children who gained more weight, activation in the part of the decision making network that deals with the salience of food do not decrease or may even increase in response to health considerations. This was accompanied with fewer healthy choices in children who had gained more weight. The incentive-sensitization theory of obesity (Burger and Stice, 2011) states that after repeated overeating episodes, conditioning occurs which leads to hyper-responsivity of regions that encode incentive salience of food cues (Burger and Stice, 2011). Thus, as children repeatedly overeat and as a consequence of that weight gain, they may become more attentive to foods. Our results suggest that this increased salience of foods may diminish the positive effects of attending to the healthiness of foods.

Our finding that developmentally younger children and children with a higher current body mass have less activation in self-control areas when accepting foods is in line with previous findings that reduced executive function predicts overweight in children (Wirt et al., 2015). Furthermore, given that children who had gained weight were less responsive to considering the healthiness of foods during choice, this could suggest that

Table 6
Brain regions with significant correlation with BMI Cole score change during the food choice task.

Brain region[a]	Side	Cluster size	x	y	z	Z-score
Yes vs. no						
Positive correlation with BMI Cole score change						
Whole brain						
Calcarine sulcus	R	149	24	−66	9	4.10
Lingual gyrus	R		9	−54	3	3.81
Lingual gyrus	R		15	−42	0	3.75
Calcarine sulcus	L	144	−24	−66	9	4.09
Middle occipital gyrus	L		−33	−72	18	3.92
Lingual gyrus	L		−15	−57	0	3.82

[a] Peaks listed are significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent = 57 voxels, 3 × 3x3 mm voxels). L, Left; R, right.

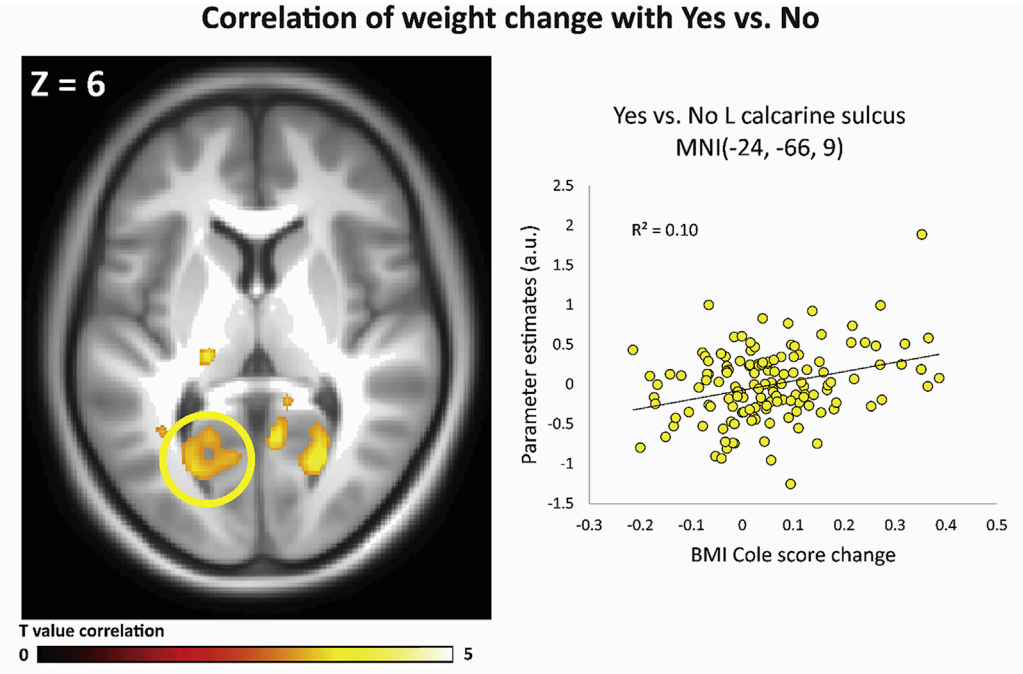

Fig. 3. Correlation of weight (BMI Cole score) change with modulation of choice activation by yes vs. no independent of condition. BMI Cole score change is in BMI Cole score points per year. Yellow circle denotes positive correlation with BMI Cole score change. Peaks listed are significant at the $p < 0.05$ level based cluster level corrections across the whole brain (individual voxel threshold = $p < 0.001$, cluster extent threshold > 57 voxels, 3 × 3x3 mm voxels).

children who need help the most i.e. younger children and children who are gaining weight or who already have overweight, may be least susceptible to health interventions. In particular, weight loss interventions that rely on the ability of children to exhibit self-control, or interventions that steer attention towards health aspects of food, may be less effective in these children. Different types of interventions, for example based more on adaptations of the obesogenic environment, such as limiting the availability of options for unhealthy behavior, may bypass the need for self-control (Marteau et al., 2012), and could thus be a more effective approach. Alternatively, interventions that are aimed at improving self-control in children may also positively affect their dietary choices (Stautz et al., 2016). Moreover, the indications of altered salience of food in children earlier in pubertal development, children with a higher current body mass and children who have gained weight, could possibly be targeted with tasks aimed to change implicit reactions to food to make them less salient (Folkvord et al., 2016). Further research should determine the relationship between the neural correlates of food choice and the effectiveness of health interventions to investigate the validity of these hypotheses.

The current study had several limitations. Firstly, we did not include equal numbers of children per pubertal stage; a lower number of younger children was included. Future studies should include a more balanced sample when comparing age/pubertal stage differences. Furthermore, we did not directly measure self-control with our food choice task. We hypothesize that the differences in dlPFC activation found are related to self-control, but future studies should address this by using a task that involves active self-control during food choice.

In conclusion, for children in earlier pubertal stages and children who have gained more weight the positive effect of considering the healthiness of foods on their choices is smaller. Furthermore, children in earlier pubertal stages and children with a higher body mass have less activation in an area important for self-control during food choice. Pubertal development, current body mass and body mass history influence the effect of health considerations on brain areas involved in saliency and motivation. Thus, the effectiveness of interventions that rely on self-control or that call attention to health aspects of food could possibly be lower in younger children, children who are relatively gaining weight and children with overweight. Instead, interventions aimed at altering the obesogenic environment or at improving self-control could be more effective in preventing weight gain in children and curbing childhood obesity.

Acknowledgements

This work was done as part of the IDEFICS (http://www.idefics.eu) and I.Family studies (http://www.ifamilystudy.eu/). We gratefully acknowledge the financial support of the European Commission within the Sixth RTD Framework Programme Contract No.016181 (FOOD), and the Seventh RTD Framework Programme Contract No. 266044. The authors were financially supported by the European Union Seventh Framework Programme (FP7/2007–2013) under Grant Agreements 266408 (Full4Health), 266044 (I.Family) and 607310 (Nudge-It). G. Orsi was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116016.

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