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ORIGINAL RESEARCH

Cognitive regulation of food intake associated with weight management and obesity prevention

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Abstract

Obesity is a major threat to the health of the nations and its prevention has been considered as one of the main public health program in many countries around the world. It is a complex epidemic problem that social and cultural factors play an important role in obesity epidemic. Specifically, environment that elevates unhealthy eating habits is the main cause of weight gain. The ability to control eating to prevention weight gain is called self-regulation which is one of the cognitive concepts. In order to better understand the functional brain response in self-control areas, the aim of this research was investigating brain activity in response to palatable food. In this study, a normal weight woman was selected and her functional magnetic resonance imaging scans (viewing food and non-food images) were used for analysis. Neural response in some priori specified regions including the dorsolateral and medial prefrontal cortex (DL-PFC/mPFC), inferior frontal gyrus (IFG) and the mid-ventrolateral prefrontal cortex (vlPFC) was assessed. A new developed Bayesian tool based on integrated nested Laplace approximation (INLA) was applied for inferences. We examined the effect of food > non-food by defining a contrast vector c = (1, -1, 0)/ 2. We then computed the posterior probability map based on two thresholds (γ_e and γ_p). The value of γ_e is set to 1% the global mean signals and the value of the probability threshold is set to $\gamma_p = 0.95$. The results showed greater activation in responses to food versus non-food stimuli in regions DL-PFC/mPFC, IFG and mid- vlPFC.
Findings represent evidence for counteractive control processes in response to food cues in the brain that it might be helpful to incorporate cognitive reappraisals in obesity prevention via weight management.

Abbreviations:
functional Magnetic Resonance Imaging (fMRI); Generalized Linear Model (GLM); Integrated Nested Laplace Approximation (INLA); Posterior Probability Maps (PPMs)

Introduction

Health care is the maintenance or improvement of health via the prevention, diagnosis, and treatment of disease, illness, injury, and other physical and mental impairments in people (WHO 2013).

Almost one-third of the US population is clinically obese (BMI ≥30 kg/m^2) and this trend has affected all ethnic and socioeconomic groups (Martin *et al.* 2010). Obesity is not only a risk factor for hypertension, cardiovascular disease, diabetes, stroke and cancer but also is considered as a disease itself. So it is a major threat to the health of the nations and its prevention has been considered as one of the main public health program in many countries around the world (Yokum & Stice 2013).

Obesity is a complex epidemic problem. Social and cultural factors play an important role in obesity epidemic. Specifically, environment that elevates unhealthy eating habits (calorie-dense and low nutrient-density foods and meals such as fast foods) is the main cause of weight gain. environment has a huge impact on the rising numbers of overweight and obese people (Volkow *et al.* 2011; Spetter *et al.* 2017). The ability to regulate and control different behaviors such as eating to prevention weight gain is called self-regulation which is one of the social cognitive concepts (Reed *et al.* 2016).

In addition to environmental factors, individual factors are also important for obesity. Based on literature, between 45% and 85% of the variability in BMI are caused by genetic factors. Although genetic studies have manifested mutations in obese population, obesity is seemed to be under polygenic control (Volkow *et al.* 2011). The limited statement of the variance from these genetic studies is likely to represent the complex interactions between genetics factors and the environment where food is widely available as a substantial reward that promotes eating (Volkow *et al.* 2011). Number of processes in the brain, such as homeostatic mechanisms, motivation, cognitive control and decision making influence on food intake. Recently researchers have been interested in characterizing the brain's role in appetite, food motivation and obesity (Smeets *et al.* 2012). Functional neuroimaging studies have assessed brain mechanisms underlying food intake in relation to weight management. Some cortical brain regions (orbitofrontal cortex (OFC), cingulate gyrus (ACC) and insula), neurotransmitter systems (dopamine, serotonin, opioids and cannabinoids), several limbic (nucleus accumbens (NAc), amygdala and hippocampus) and the hypothalamus are involved in the rewarding effects of food (Petrovich *et al.* 2005; Volkow *et al.* 2011). Critically, elevated reward activation to palatable food cues, cues signaling impending unhealthy food images, and high-fat/sugar images predict future weight gain (Stice & Yokum 2016).

In brain research, functional Magnetic Resonance Imaging (fMRI) has become a useful tool that uses blood-oxygen level dependent (BOLD) as a method for determining neuronal activity.

The images collected in BOLD fMRI experiments generally have spatial resolution (millimeters) and temporal resolution (seconds), so we encounter to massive amounts of highly complex correlated data (Huettel *et al.* 2004). Respect to data structure, classical generalized linear model (GLM) does not seem proper for consideration data properties, also classical GLM suffers from multiple comparisons problem and lack of power to detect true effects (Ishwaran & Rao 2003, Marchini & Presanis 2004). A potential risk for fMRI data analysis is false positive and false negative results which must be controlled (Bartsch *et al.* 2006; Haller & Bartsch 2009, Magerkurth *et al.* 2015). Literature discussed this problem and suggested solutions. Considering these issues, several Bayesian GLM alternatives to the classical GLM have been proposed (Johnson *et al.* 2013; Magerkurth *et al.* 2015). The main challenge about Bayesian approach is its computational aspect so standard Markov chain Monte Carlo (MCMC) methods are typically too time-consuming (Woolrich *et al.* 2004). Alternative methods for MCMC have been introduced such as variational Bayesian (VB) and integrated nested Laplace approximation (INLA) techniques which resulted in computational advances. However, it has been well-shown that VB approach underestimates posterior variance but INLA method can estimate approximations to the posterior distributions accurately (Wang & Titterington 2005; Rue *et al.* 2009, Rue *et al.* 2017; Sidén *et al.* 2017). Accordingly, INLA is applied for inferences. In addition to areas involved in visual attention and reward processing, we assume self-regulation areas in response to food cues will be activated in individuals with a weight watching purpose. Some priori specified regions of interest based on recent studies include the dorsolateral and medial prefrontal cortex (DL-PFC/mPFC), inferior frontal gyrus (IFG) and the mid-ventrolateral prefrontal cortex, which have been consistently involved in the exertion of self-control (Casey *et al.* 2011, Hare *et al.* 2011; Heatherton & Wagner 2011).

The current research focuses on localization of mentioned areas in response to palatable food. A new developed Bayesian tool based on INLA is used for inferences (Rue *et al.* 2009).

Materials and methods

Participant and experimental design

A normal weight woman was chosen. In this experimental design sequences of food and non-food images on a white background were shown. The accession number of data is ds000157 in OpenfMRI database and detailed explanation of data is published elsewhere (Smeets *et al.* 2013).

Functional Magnetic Resonance Imaging

Functional whole-brain T2 weighted images were acquired by using a gradient echo 2D-echo planar imaging sequence (64×64, repetition time=2100 ms, echo time=23 ms, flip angle=72.5, FOV=208×119×256 mm, SENSE factor AP=2.4, 30 axial 3.6 mm slices with 0.4 mm gap, reconstructed voxel size=4×4×4 mm). In each functional run 370 scans were collected. Also a high resolution T1-weighted anatomical MRI scan was made (3D gradient echo sequence, repetition time=8.4 ms, echo time=3.8 ms, flip angle=8, FOV=288×288×175, 175 sagittal slices, voxel size=1×1×1mm). This high-resolution anatomical image was used for image registration and anatomical localization.

Data processing and statistical analysis

First data was preprocessed using the standard preprocessing steps including slice-timing, realign, smoothing, filtering (Glasser, Sotiropoulos *et al.* 2013). Preprocessing was conducted using SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), after data preparation, Bayesian GLM approach was fitted as follow.

Bayesian GLM approach

Suppose that there are N voxels and a sequence of t=1.... .T time points are extracted from each voxel. For a subject, the following GLM model was fitted (Mejia, Yue *et al.* 2017):

$$\mathbf{y}=\sum_{k=0}^{K}\mathbf{X}_k\boldsymbol{\beta}_k+\boldsymbol{\varepsilon}, \qquad \boldsymbol{\varepsilon}\sim \mathrm{N}(0,\mathbf{V}), \tag{1}$$

where, y is an TN ×1 vector comprising the fMRI time series of all voxels, and the X_k is TN ×N design matrices for the activation amplitudes β_k for k = 0, … , K, where K is the number of task under investigation. The matrix V is a T×T covariance matrix for an AR(p) process, where p is the degree of autoregressive.

The spatial correlation is considered via the unweighted graph-Laplacian (UGL) prior on each β_k. UGL is defined as below (Sidén *et al.* 2017):

$$\boldsymbol{\beta}'_{k\cdot}|\alpha_k \sim \mathrm{N}\left(0, (\alpha_k \mathbf{D}_{\boldsymbol{\beta}})^{-1}\right), \tag{2}$$

where D_β is a fixed spatial N×N precision matrix and $\alpha = (\alpha_1.....\alpha_k)'$ are hyper parameters to be estimated from the data. There are several choices for D_β but this study considers UGL, which has the number of adjacent voxels on the diagonal for each voxel and $D_\beta(i.j)= -1$, on the condition that i and j are adjacent. When modeling each 2D slice separately, for voxels in the interior part of the brain there exist 4's on the diagonal (Sidén *et al.* 2017). The full conditional distribution of each β_k was obtained using Bayesian computation tool based on INLA, which is implemented in the R-INLA package (Rue *et al.* 2009).

To consider the temporal correlation of time series, the fMRI time courses were first pre-whitened by assuming an AR(p) process on the residuals from a classical GLM with uncorrelated errors. Regarding data, we set *p*=1 (Bollmann *et al.* 2018). The detailed explanations of pre-whitened approach are given elsewhere (Monti 2011).

Six rigid body realignment parameters were included in the model as nuisance covariates to account for noise due to subject motion. Furthermore, for considering scanner drift, linear and quadratic time terms were added to model.

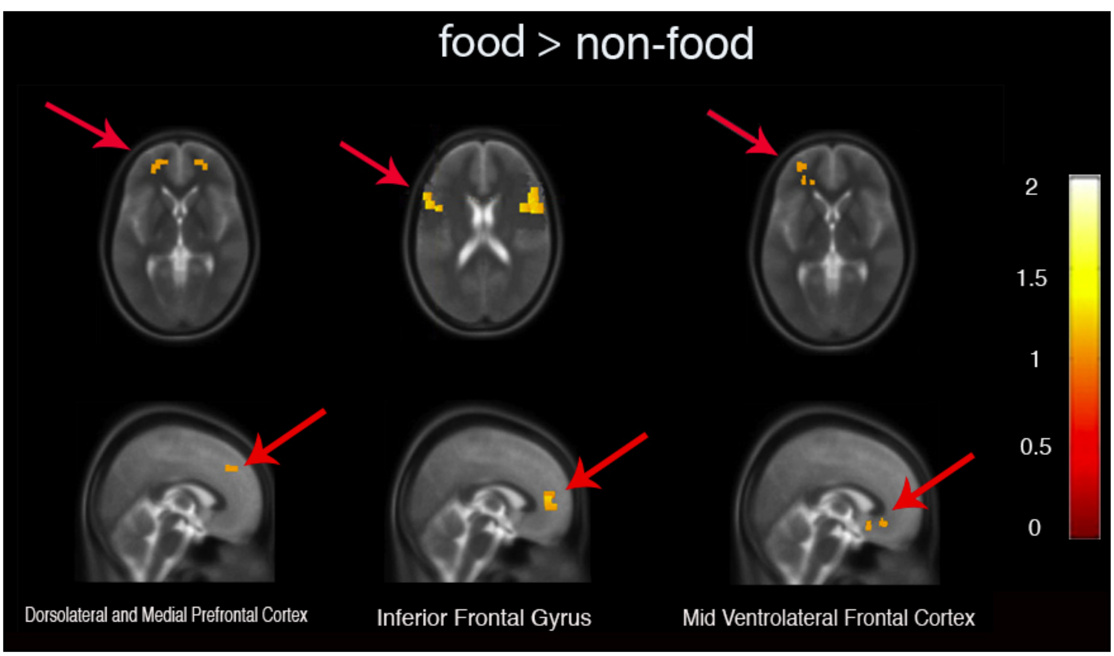

Fig. 1. Posterior mean estimates of food vs non-food on the 15th, 20th and 14th plane out of 40 planes along the z-axis for DL-PFC/ mPFC, IFG and mid-VLPFC. The first and second rows show results in Axial and Sagittal views, respectively.
DL-PFC/ mPFC: dorsolateral/ medial prefrontal cortex
IFG: inferior frontal gyrus
mid-VLPFC: mid-ventrolateral prefrontal cortex

After fitting model and estimating β , the posterior probability maps (PPMs) on the effect of food were created, we did it by defining a contrast vector as c= (1, -1, 0) /2 then multiplied this vector by β, where β denotes the vector of regression coefficients at a given voxel. Effect size c^T β measures the effect of food versus non-food in the experiment. The posterior distribution of the contrast was then shown across voxels using a PPM. This map is based on two thresholds, the first being an effect size threshold γ_e and the other being a probability threshold γ_p. The value of γ_e is set to a constant so that c^T β greater than 1% the global mean signals (across voxels) are remarked as "activated." The value of the probability threshold is set to be $\gamma_p = 0.95$. We then computed the posterior distribution $P(c^T \beta > \gamma_e | \text{Data})$ for each voxels and we highlighted those voxels where the posterior probability was greater than $\gamma_p = 0.95$ (Penny *et al.* 2005; Teng *et al.* 2018).

A region of interest (ROI) analysis was conducted on regions; the DL-PFC/ mPFC, the IFG and the mid-vlPFC. Posterior mean estimates and posterior probability map were mapped on a standardized single T1 template in SPM (Oishi *et al.* 2009). Data was prepared by programming in MATLAB R2016b software and then model fitting was performed using R 14.2 software. The INLA is now available through INLA package of the R software (http://www.r-inla.org).

Results

The ROI analysis is performed after pre-processing the data. Brain activation maps are viewed using the xjView (http:/www.alivelearn.net/xjview). The mentioned regions are related to self-regulation skills. The reason to perform an ROI analysis is to avoid the difficulty faced in discerning the pattern of activity across conditions from an overall map. The other reason is to limit the testing to a region that is functionally defined on the basis of interested functional regions. After estimation temporal correlation via pre-whitening approach, the INLA method is applied to Gaussian likelihood function with uncorrelated errors and the posterior estimates are obtained.

Image depicting the estimated coefficients is shown in Fig. 1 in two different Axial and Sagittal views. The estimates of c^T β for food > non-food contrast were displayed on the 15^{th}, 20^{th} and 14^{th} plane out of 40 planes along the z-axis for the DL-PFC/ mPFC, the IFG and the mid- vlPFC, respectively. As shown, participant under study showed greater responses to food vs. non-food stimuli in these regions.

Respect to activations, we next examined, the effect of food > non-food by defining a contrast vector c = (1, -1, 0)/ 2. The value of γ_e is set to 1% the global mean signals (across voxels) and the value of the probability threshold is set to be $\gamma_p = 0.95$. We then computed the PPMs, results are shown in Fig. 2.

Three-dimensionally rendered SPM images representing the areas with higher reactivity of each region to food > non-food contrast (reflected in the activation of DL-PFC /mPFC, IFG and mid-VLPFC). In terms of timing, INLA takes 2 minutes with all computations performed on a MacBook Pro with 3.2-GHz and 8-GB memory.

Discussion

In this research, the brain activation in response to palatable food was investigated using INLA method in some pre-defined regions including the DL-PFC/ mPFC, IFG and mid-VLPFC. Our findings were consistent with previous studies. The results showed that self-regulation areas response to palatable foods in individual who is careful about her weight. Different

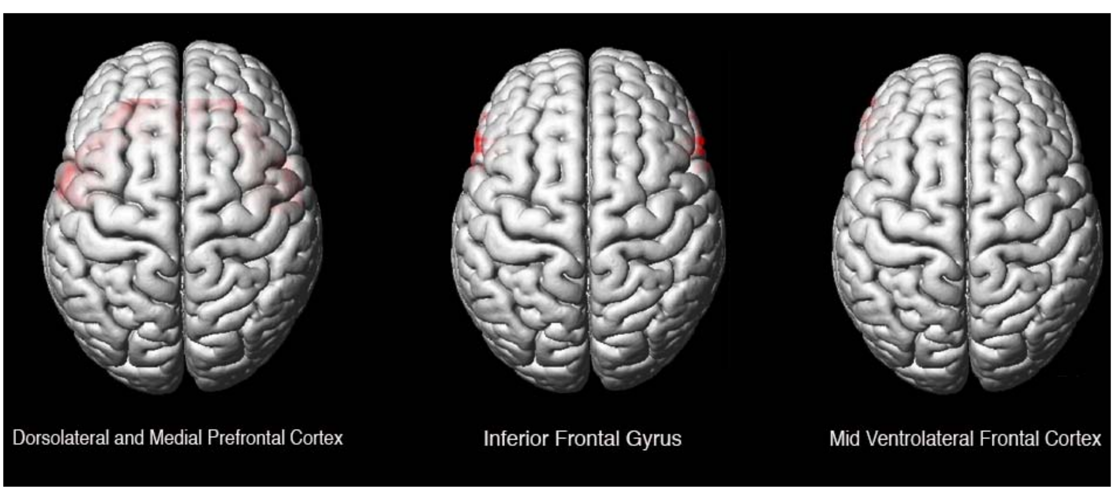

Fig. 2. Posterior probability map showing the activated voxels for DL-PFC/ mPFC, IFG and mid-VLPFC, with an effect size threshold of 1% greater than the global mean and a probability threshold of 95%.
DL-PFC/ mPFC: dorsolateral/medial prefrontal cortex
IFG: inferior frontal gyrus
mid-VLPFC: mid-ventrolateral prefrontal cortex

literatures reported the prefrontal cortex as the most important area related to self-regulation skills (Miller & Cohen 2001; Goldberg 2002; Curtis & D'esposito 2003). The orbitofrontal cortex, lateral PFC and the anterior cingulate cortex (ACC) are three main areas of PFC (Banfield *et al.* 2004; Heatherton & Krendl 2009). Localization of brain in task related fMRI data and in response to food cues has been addressed in several studies. Brain activation by consideration of weight management in some areas such as the lateral PFC, IFG and the ACC was assessed by Smeets *et al.* and they concluded higher activation in mentioned regions (Smeets *et al.* 2013). A meta-analysis of neural responses to food images was conducted and the brain response to high and low calorie foods was investigated. The results showed regions that lay within the visual system (occipital lobe) have significant activations. The most robust activation convergence was in the right fusiform gyrus. Lateralized convergent activations were reached in the left insula, right postcentral gyrus, right precuneus, left IFG, left middle occipital gyrus and left hippocampus. Bilateral convergent activations were observed in the fusiform gyrus, declive, parahippocampus and superior temporal gyrus (Huerta *et al.* 2014). Another study examined neural response to food choices between high and low calorie foods versus non-food images. Stronger signals in the left insula, superior temporal sulcus and posterior cingulate gyrus were reported (Charbonnier *et al.* 2015). Previous fMRI study in healthy weight adults reported greater responses in the amygdala, anterior fusiform gyrus and parahippocampal gyrus when individuals were in a hungry state compare to a satisfied state (Martin *et al.* 2010). Our finding that foods elicited elevated (visual) attention is well confirmed in the literature. A recent study identified brain regions associated with dietary self-control using a coordinate-based meta-analysis on fMRI studies. They reported brain regions including the anterior insula, inferior and middle frontal gyrus, supplementary motor cortex and parietal cortices which related to dietary self-control (Bossier *et al.* 2017). Also another meta-analysis has shown food images elicit stronger activation in visual areas than non-food images (van der Laan *et al.* 2011). Importantly, as the activation of self-control upon confrontation with food cues is representative of adaptive self-regulation mechanisms, our predictions particularly apply to participant who would be classified as a successful self-regulator (Fishbach *et al.* 2003; Papies *et al.* 2008). Accordingly, woman in this study had normal weight so she was successful in regulating her food intake (Meule *et al.* 2012). In contrast, it is plausible that our results would not be confirmed in overweight or obese individuals who are unsuccessful at regulating food temptations. A novel approach for Bayesian inferences was used to investigate the effect of food cues on neural response of regions important to the regulation of human appetite and food intake.

In this study, a more recently developed Bayesian inference tool based on INLA was applied. The INLA method can compute approximations to the posterior distributions accurately and capable to handle large data sets. Also it performs computation much more quickly than traditional Bayesian approach such as MCMC and can be easily conducted using the R-INLA package. A recent study was conducted on cortical surface fMRI data from the Human Connectome Project (HCP) which INLA method was applied for inferences (Mejia *et al.* 2017).

A major limitation of the current work is the regional based assessment so it is therefore important to conduct whole brain analysis to investigate more related regions. We performed single subject analysis, it is also possible to extend this Bayesian approach for including more subjects in analysis. Based on literature reviews only few neuroimaging studies have investigated the relations between genes, brain and behavior while many polymorphisms have been implicated in body weight control. It is well stablished that genetic factors have important roles on neural processing of self-regulation areas, so consideration of genetic information will be useful to assess the self-control cognitive process (Smeets *et al.* 2012).

Conclusion

Findings represent evidence for counteractive control processes in response to food cues in the brain that it might be helpful to incorporate cognitive reappraisals in obesity prevention via weight management. Since obesity prevention programs have not reached clinically meaningful reduction in future weight gain, one of the main priority of public health is to introduce effective programs.

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Disclosure

The authors declare no conflicts of interest.

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