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The Impact of Replacing Sugar- by Artificially-Sweetened Beverages on Brain and Behavioral Responses to Food Viewing – An Exploratory Study

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ABSTRACT

Several studies indicate that the outcome of nutritional and lifestyle interventions can be linked to brain 'signatures' in terms of neural reactivity to food cues. However, 'dieting' is often considered in a rather broad sense, and no study so far investigated modulations in brain responses to food cues occurring over an intervention specifically aiming to reduce sugar intake. We studied neural activity and liking in response to visual food cues in 14 intensive consumers of sugar-sweetened beverages before and after a 3-month replacement period by artificially-sweetened equivalents. Each time, participants were presented with images of solid foods differing in fat content and taste quality while high-density electroencephalography was recorded. Contrary to our hypotheses, there was no significant weight loss over the intervention period and no changes were observed in food liking or in neural activity in regions subserving salience and reward attribution. However, neural activity in response to high-fat, sweet foods was significantly reduced from pre- to post-intervention in prefrontal regions often linked to impulse control. This decrease in activity was associated with weight loss failure, suggesting an impairment in individuals' ability to exert control and adjust their solid food intake over the intervention period. Our findings highlight the need to implement multidisciplinary approaches when aiming to help individuals lose body weight.

KEYWORDS

EEG; sugar-sweetened beverages; food; cognitive control; prefrontal cortex; food liking

ABBREVIATIONS

ASB	Artificially sweetened beverage
BMI	Body mass index
DPFC	Dorsal prefrontal cortex
EEG	Electroencephalography
GFP	Global field power
HF/NSW	High-Fat / Non-Sweet
HF/SW	High-Fat / Sweet
IPL	Inferior parietal lobe
ITI	Inter-trial interval
LAURA	Local autoregressive average
LF/NSW	Low-Fat / Non-Sweet
LF/SW	Low-Fat / Sweet
LPFC	Lateral prefrontal cortex
MNI	Montreal Institute template brain
NNS	Non-nutritive sweeteners
PreCG	Pre-central gyrus
ROI	Region of interest
SSB	Sugar-sweetened beverage
TMS	Transcranial magnetic stimulation
TW	Time window
VEP	Visual evoked potential

INTRODUCTION

Pre-ingestive responses to food viewing are of particular importance as visual features of foods (e.g. perceived caloric load by macronutrient identification) become conditioning stimuli able to trigger food wanting or control over food intake (Berridge, 2009; Dagher, 2012). In healthy individuals, the exposure to food cues (e.g. visual) triggers complex brain processes, i.e. categorizing what is being perceived, integrating the salience of external food cues with internal metabolic needs, and evaluating the physiological adequacy to guide food intake (Van der Laan et al., 2011). The pre-ingestive integrative treatment of food-related information is essential to promote need-adequate intake behaviors, and relies, among other things, on homeostatic and reward areas (hypothalamus, insula and the limbic system; Suzuki et al., 2010). However, this regulatory system also requires inputs from brain areas involved in attentional control and decision-making processes (i.e. parietal and dorsal prefrontal areas as part of the executive function network; Seeley et al. 2007) to counterbalance the salient properties inherent to palatable foods and prevent food intake beyond homeostatic needs.

Increasing evidence suggests that weight gain may be a 'brain disorder' in which pre-ingestive homeostatic and control mechanisms, involved in the regulation of food intake according to body energy needs, are overridden by hedonic drives towards abundant palatable energy-dense foods (Berthoud, 2011; Morris et al., 2015). In overweight/obese individuals, neural activity in the above-mentioned brain areas in reaction to food cues have been shown to be altered in comparison to normal-weight individuals, and may account for an overconsumption of palatable energy-dense foods (see Garcia-Garcia et al., 2013; Martin & Davidson, 2014 and Pursey et al., 2014 for reviews). In support of this assumption, several functional neuroimaging studies have identified changes in brain responsiveness to food cues due to longitudinal nutrition and lifestyle interventions. For instance, Murdaugh and colleagues (2012) showed that hyper-reactivity to high-calorie food images in brain areas involved in reward valuation was predictive of individuals' short- and longer-term failure in a weight-loss program. Similar findings were reported by Weygandt and colleagues regarding impulse control mechanisms, i.e. greater neural activity to food viewing in dorsolateral prefrontal brain region involved in cognitive control was associated with subsequent weight loss (2013) and prevention of weight regain (2015).

These studies indicate that the outcome of nutritional and lifestyle interventions can be linked to brain 'signatures', both from the homeostatic-salience and the executive function networks. However, these studies considered 'dieting' in a rather broad sense, and no study so far investigated modulations in brain responses to food cues in the context of a nutritional intervention specifically aiming to reduce sugar consumption. Yet, the consumption of sugar, more specifically of sugar-sweetened beverages (SSBs), has been associated with the high prevalence of obesity worldwide, and reduction of SSB consumption has become a prime target for body weight control interventions and policies (Bray et al., 2004; Popkin & Nielsen, 2003; SACN report, 2015; Vartanian et al., 2007). SSBs have been proposed to affect body weight through a variety of mechanisms (DiMeglio & Mattes, 2000; Malik et al., 2006); but how a reduction in sugar intake impact hedonic drives and impulse control to foods remains poorly understood.

The goal of our study was to investigate changes in behavioral and brain responses to visual solid food cues occurring over a 3-month intervention targeting sugar consumption, i.e. the replacement of SSBs by artificially sweetened equivalents. In parallel with expected individuals' weight loss, we hypothesized that neural activity to food viewing would increase from pre- to post-intervention in

brain regions associated with control over food intake. Moreover, we expected a decrease in neural activity in brain regions associated with salience and reward attribution, together with decreased visual like ratings (i.e. behavioral responses). Both brain and behavioral outcomes would be most pronounced in response to high-calorie sweet food viewing as compared to other food types. Spatio-temporal brain response modulations to the viewing of food types differing in their fat content and taste quality were therefore investigated before and after a 3-month intervention period using high-density electroencephalography (EEG) and electrical neuroimaging analyses (Toepel et al., 2009; Bielser & Crézé et al., 2016). In parallel, behavioral ratings of visual food appreciation served to assess intervention-induced modulations in food liking.

MATERIAL AND METHODS

Participants

Fourteen healthy volunteers (6 women) were recruited for this study, i.e. intensive consumers of SSBs on a daily basis (between 2 and 6 cans of 33cl of soft drinks, corresponding to 70-210g of added sugar per day). The volunteers were a subsample of participants of a clinical intervention conducted at the Department of Physiology of the University of Lausanne targeting metabolic changes (Campos et al., 2015; 2017). Their age ranged from 18 and 40 years (mean age ± SEM = 27.1 ± 1.6), and body mass indices (BMI) from 21.2 to 35.4 kg/m^2 (mean BMI ± SEM = 28.3 ± 1.3 kg/m^2). All volunteers had normal or corrected-to-normal vision. None of the participants had current or prior diabetes, cardiovascular, kidney, hepatic, neurological or psychiatric disease. Further exclusion criteria were particular diets (e.g. vegetarianism), exercising for more than 3 hours per week and/or walking more than 1 hour per day, having gained or lost more than 4kg in body weight during the last 12 months, current medication or drug-taking, and consuming more than 10g of alcohol per day. Women were excluded when pregnant or when having a desire for pregnancy. All volunteers were informed about the procedures and signed a written consent previously approved by the Ethics Committee of the Canton of Vaud.

General procedure

Overall, the study lasted 16 weeks and comprised of two sessions of behavioral assessments and EEG recordings (Figure 1A). First, all participants underwent a 4-week run-in period where they were asked to consume a regular amount of sugar-sweetened beverages per day, in line with their habitual consumption. Second, they underwent a 12-week intervention period. Over this period, participants had to continue drinking the same amount of soft drinks per day as during the run-in period, but the commercially available artificially sweetened equivalent (artificially sweetened beverage; ASB) of their usual beverage. That is, volunteers consumed a mix of aspartame, cyclamate, acesulfam K and sucralose. Over the 16 weeks, volunteers were asked to drink only beverages distributed to them by the Department of Physiology, University of Lausanne. Their food and non-caloric beverage intakes were otherwise left *ad libitum*. Compliance to the intervention was monitored by counting the number of returned soda cans as well as from urine samples pre-, mid-, and post-intervention (Campos et al., 2015).

In the end of the 4-week run-in period and in the end of the 12-week intervention period (i.e. PRE- and POST-intervention session respectively), participants reported to the laboratory for the assessment of behavioral and brain responses to food viewing, by means of visual appreciation ratings and EEG recordings. Participants were instructed and reported to have eaten a normal

breakfast or lunch, and assessments took place 2-3 hours after the last food intake. Before and after each of the EEG recording session, participants rated their hunger level by means of a visual analog scale anchored to 0-100%. Differences in hunger across the EEG session were analyzed using a paired student t-test (two-tailed). Additionally, participants' pre-prandial body weight had been measured PRE- and POST-intervention (Campos et al., 2015), and changes from PRE- to POST-intervention sessions were investigated using a paired student t-test (two-tailed).

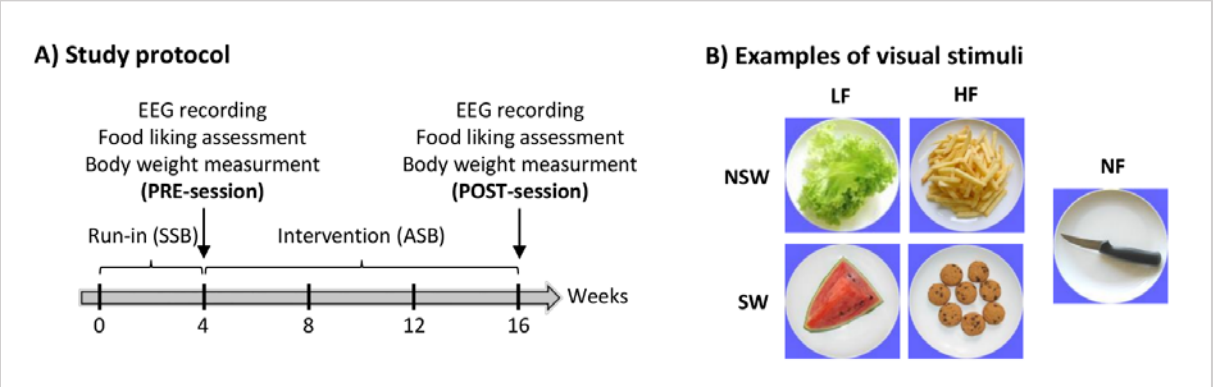

Figure 1: (A) *Timeline of overall experiment conducted overt 16 weeks. Electroencephalography (EEG) recordings, food like ratings and body weight measurements were performed before (PRE-session) and after (POST-session) the intervention.* ***(B)*** *Exemplar stimuli shown during EEG recordings and food like rating task. Food image categories differed with respect to fat content and taste quality of the displayed foods. SSB: sugar-sweetened beverage. ASB: artificially sweetened beverage. LF: low-fat. HF: high-fat. NSW: non-sweet. SW: sweet. NF: task-relevant non-food images.*

Visual stimuli and online behavioral task

In each EEG recording session, color photographs either containing food (360 items) or non-food objects (180 items) were shown to participants on a computer screen. Four types of food were presented, differing in fat content and in taste quality, i.e. Low-Fat/Non-Sweet (LF/NSW), Low-Fat/Sweet (LF/SW), High-Fat/Non-Sweet (HF/NSW) and High-Fat/Sweet (HF/SW) (Figure 1B). The fat content of low-fat foods ranged from 0 to 5g of fat per 100g (mean fat content ± SEM = 0.89 ± 0.13g), and from 10.68 to 81.10g of fat per 100g for high-fat foods (mean fat content ± SEM = 27.12 ± 1.39g). Non-food pictures consisted of kitchen utensils and were relevant for the online behavioral task only (see below). Pictures were controlled for low-level visual features (Knebel et al., 2008).

Data recordings took place in a sound attenuated booth and images were presented centrally on a 19'' computer screen for 500ms each, in 6 consecutive blocks lasting 3-4 minutes. Each block contained pictures of food and non-food items in a pseudo-randomized order controlled by the E-prime software (Psychology Software Tools, Inc., Pittsburgh, USA). Participants were asked to categorize food from non-food pictures via button-press, thus remaining uninformed about the various food categories viewed (Toepel et al., 2009). They were instructed to perform as quick and accurate as possible. Following the response, the Inter-Trial-Interval (ITI) randomly varied between 250 and 750ms to avoid anticipatory responses. During the ITI, a fixation cross was centrally displayed on screen to avoid eye movements.

EEG acquisition and preprocessing

Continuous EEG was recorded while participants viewed images and performed the categorization task. EEG was acquired at a sampling rate of 512 Hz using a 64-channel Biosemi ActiveTwo system, referenced to a CMS-DRL ground (see http://www.biosemi.com/pics/zero_ref1_big.gif for a detailed diagram of this circuitry). All pre-processing analyses were performed using the CarTool software (https://sites.google.com/site/fbmlab/cartool). Visual evoked potentials (VEPs) were computed over the period from -98ms to +488ms peri-stimulus epoch for each image. During single subject averaging, EEG epochs were cleaned from artifacts with a semi-automatic procedure using a 80µV rejection criterion and visual trial-by-trial inspection. Epochs containing eye blinks or other motor artifacts were manually removed. During averaging, data was band-pass filtered at 0.1 – 40Hz (plus at 50Hz for smoothing edges). First, VEPs were averaged for each single subject, food category (LF/NSW, LF/SW, HF/NSW and HF/SW) and recording session (PRE- and POST-intervention). Electrodes with artefactual signals were then interpolated (Perrin et al., 1987). In a second step, group-average VEPs were calculated for each food category and session, while baseline-correcting over the pre-stimulus period and recalculating the VEPs to an average reference (Murray et al., 2008).

EEG analyses and source estimations

In order to determine time windows of interest for analyzing intervention-induced changes in brain responses to food viewing, we identified peaks in the Global Field Power (GFP) in the group-average responses and validated their timing in the single-subject responses. The GFP is a reference-independent measure of the global strength (i.e. amplitude) of VEPs over the electric field over time. Mathematically, it is calculated as the standard deviation of the electric field amplitude across all electrodes at a given time point. GFP peaks are representative of maximally synchronized neural activity underlying cognitive processes within a given condition (Lehmann & Skrandies, 1980; Michel & Murray, 2012; Murray et al., 2008). Thus, periods of maximal GFP served as a rational for the further investigation of intervention-induced changes in neural source estimates (Toepel et al., 2009; 2015).

Over the time windows of interest, estimations of neural source activity based on the head-surface recorded VEPs served to determine brain regions showing intervention-induced modulations as a function of the viewed food category. For this purpose, the neural activity was analyzed over time windows of interest using a local autoregressive average (LAURA) distributed linear inverse solution (Michel et al., 2004). That is, mean amplitudes of activity were calculated for each of the 3005 solution points of an inverse solution matrix based on a realistic 3D head model (resolution of 6x6x6 mm^3) over each time window of interest, as in former studies (Bielser & Crézé et al., 2016; Lietti et al., 2012; Toepel et al., 2009; 2014; 2015). The output of the algorithm is one scalar value ($\mu A/mm^3$) per solution point per food viewing condition and time window. As the goal of our study was to investigate the effects of a diet intervention on the spatio-temporal brain dynamics to food viewing, we focused the analyses on the relative change in neural signal from PRE- to POST-intervention recording sessions. For this purpose, the PRE-intervention neural activity strength (in $\mu A/mm^3$) at each node of the solution point matric was first subtracted from the POST-intervention signal in each participant and for each food category viewed. The difference values obtained for each source node were then multiplied by 100 and divided by the mean PRE-intervention activity across all nodes of the solution point matrix in each individual and each food category viewed. This approach accounts

for inter-subject variability in neural activity at baseline, since relative (% change) and not absolute values entered the analyses.

For each time window of interest, statistical analyses first comprised of whole-brain repeated measure ANOVAs with the within-subject factors of fat content (i.e. Low-Fat vs. High-Fat foods) and taste quality (i.e. non-Sweet vs. Sweet foods), computed on the % change in signal from PRE- to POST-intervention sessions on each node of the solution point matrix. Only regions showing a significant interaction between fat content and taste quality (extending the cluster size criterion of >10 neighbors) were considered for post-hoc region-of-interest (ROI) analyses (Toepel et al., 2009). Results were rendered on the Montreal Institute template brain (MNI) and Talairach coordinates of the area showing the maximal statistical difference between conditions are given (Talairach & Tournoux, 1988).

In each ROI showing a significant interaction, neural activity of the source node revealing maximal statistical differences (plus its 6 immediate neighbors) was extracted and averaged in each individual's data for each food category viewed. These results are visualized as bar plots, indicating pre-to-post increases or decreases in food viewing neural activity. Post-hoc paired t-tests (two-tailed) were conducted on the % change in signal from PRE- to POST-intervention to investigate how fat content and taste quality of the viewed foods relates to changes in activity. Furthermore, orthogonal one-sample t-tests (two-tailed) assessed, within each ROI and each food category, whether the % change in signal significantly differed from baseline (i.e. PRE-intervention activity). Overall, only results with $p \leq 0.05$ were considered as significant. Effect sizes (i.e. Cohen's d values) are reported for all significant results and trends. All analyses were conducted using customized Python scripts and the software tools R and STEN (Sten toolbox programmed by Jean-François Knebel from the Laboratory for Investigative Neurophysiology, CHUV and UNIL, Lausanne; http://doi.org/10.5281/zenodo.1164152).

Post-EEG assessment of visual food liking

Following each EEG recording session, participants rated their appreciation of each food image offline to test for intervention-induced modulations in liking of solid foods. All 360 food images were randomly presented in three blocks of 120 pictures. Participants were asked to rate how much they liked each viewed food on a 5-point Likert scale (1-dislike, 5-strongly liked) by button press. Pictures were displayed centrally on the same 19" computer screen, controlled by the E-prime software. For statistical analyses of these behavioral data, a mean 'liking' value was calculated for each food category, i.e. LF/NSW, LF/SW, HF/NSW and HF/SW, for each participant and session. In line with the goal of our study, we focused on the relative change in liking from PRE- to POST-intervention sessions in %. One-sample t-tests served to investigate whether the % change in liking from PRE- to POST-intervention session significantly differed from baseline (i.e. PRE-intervention session) for each food category. Overall, only results with $p \leq 0.05$ were considered as significant. All statistical analyses were conducted using the R software.

Associations between PRE- to POST-session changes in body weight, food liking and neural responses

Spearman correlation analyses tested associations between changes in neural activity induced by SSB replacement and changes in body weight as well as in food liking. Only the % change in signal in brain regions showing significant modulations in neural activity from PRE- to POST-intervention sessions

entered these additional analyses. Spearman rho values are reported only when significant ($p \leq 0.05$). All analyses were conducted using the R software.

RESULTS

Hunger level and changes in visual food liking

Average hunger ratings across each EEG recording session were 45.6 % (SEM ± 7.6) in PRE-intervention session, and 49.9 (SEM ± 6.6) in POST-intervention session, and showed no significant difference between sessions. Relative changes (in %) in the appreciation of solid foods (food like ratings) were +2.8 % (SEM ± 3.2), -2.8 % (SEM ± 2.7), +3.5 % (SEM ± 2.2) and -5.0 % (SEM ± 3.5) for LF/NSW, LF/SW, HF/NSW and HF/SW food categories, respectively. Orthogonal one-sample t-tests showed no significant changes in appreciation from baseline (i.e. PRE-intervention session) for either food category.

Changes in neural source activity to the viewing of solid foods from PRE- to POST-intervention

Figure 2A shows the GFP waveforms for all food viewing conditions over time and highlights GFP peaks, i.e. time windows of interest for further analyses. A first peak was identified between 130-160ms after food image onset, and a second peak between 280-310ms after food image onset.

Over the first time period of interest (130-160ms post-image onset), whole-brain analyses revealed interactions of fat content x taste quality on PRE- to POST-intervention % change in neural activity to food viewing in the right lateral prefrontal cortex (LPFC; Max: x=59, y=-11, z=14) and in the medial dorsal prefrontal cortex (DPFC; Max: x=-21, y=37, z=42) (Figure 2B, left panel). That is, SSB substitution differentially influenced neural activity to food viewing in these areas as a function of fat content and taste quality of the viewed foods. Modulations in neural source activity by SSB intervention in these regions of interest were further assessed by post-hoc tests. In the LPFC as well as in the DPFC, one sample t-tests for each food category (vs. baseline PRE-intervention session) showed that specifically the activity to viewing HF/SW food images was significantly lower after the SSB intervention (LPFC: $t_{13}=-2.23$; $p<0.05$; Cohen's d=-0.60; DPFC: $t_{13}=-2.37$; $p<0.05$; Cohen's d=-0.63). Between-category differences became apparent between HF/NSW and HF/SW foods (LPFC: $t_{13}=2.18$; $p<0.05$; Cohen's d=0.73 and DPFC: $t_{13}=2.18$; $p<0.05$; Cohen's d=0.70) (Figure 2C, left panel). Trends towards differences were observed between LF/NSW and HF/NSW foods ($t_{13}=-1.97$; $p=0.07$; Cohen's d=-0.63) in the LPFC, as well as between LF/SW and HF/SW foods ($t_{13}=2.14$; $p=0.05$; Cohen's d=0.73) in the DPFC region.

Over the second time window of interest (280-310ms post-image onset), an interaction of fat content x taste quality was found for pre-to-post neural activity changes in the left inferior parietal lobe (IPL; Max: x=-60, y=-27, z=37) and in the right pre-central gyrus (PreCG; Max: x=53, y=-10, z=41) (Figure 2B, right panel). One sample t-tests considering changes with respect to baseline (i.e. PRE-intervention session) showed that in particular PreCG activity in response to HF/SW food viewing tended to be increased after SSB intervention ($t_{13}=2.13$; $p=0.05$; Cohen's d=0.57). Further, significant between-category differences in intervention-induced modulations were observed between both sweet foods categories (i.e. LF/SW and HF/SW; $t_{13}=-2.47$; $p<0.05$; Cohen's d=-0.84), and trends towards differences between HF/NSW and HF/SW foods ($t_{13}=-2.06$; $p=0.06$; Cohen's d=-0.64). In the IPL, the responses to LF/SW foods differed from those to LF/NSW foods ($t_{13}=-2.93$; $p<0.05$; Cohen's d=-0.73) and to HF/SW foods ($t_{13}=2.28$; $p<0.05$; Cohen's d=0.76) (Figure 2C, right panel).

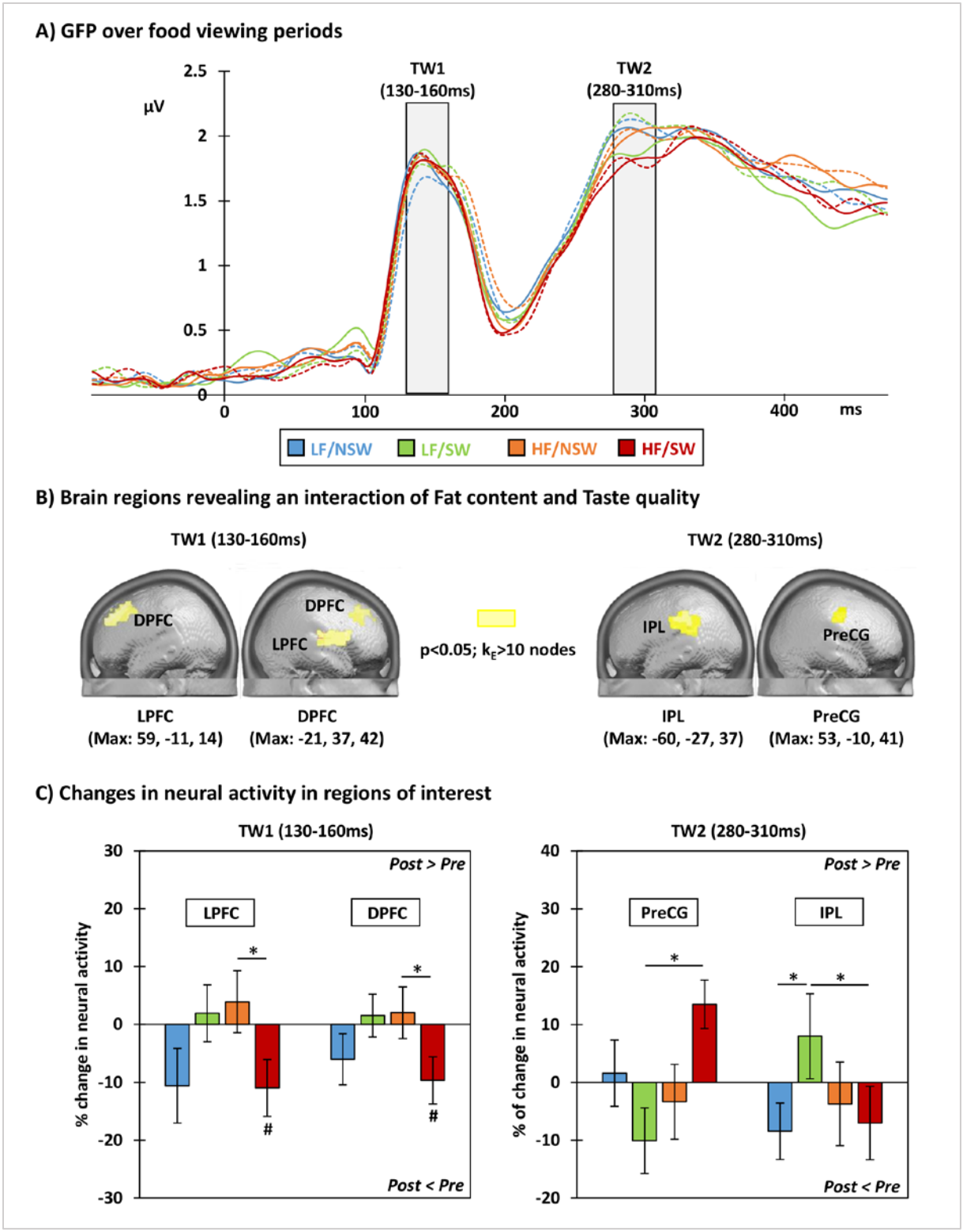

Figure 2: (A) *Group average Global Field Power (GFP) waveform for the 4 food categories over the peri-stimulus period (-98 to +488ms from image onset). Solid lines indicate GFP during the PRE-session, and dotted lines show GFP during the POST-session. Grey boxes highlight time windows (TW) of interest for subsequent analyses.* ***(B)*** *Visualization of brain regions showing an interaction of fat content x taste quality in the whole brain analyses of changes in estimated neural activity from PRE- to POST-intervention session. Talairach coordinates (x, y, z) indicate the position of the source node*

showing maximal statistical differences. ***(C)*** *Results of post-hoc analyses on changes in neural activity in each region of interest. Bar plots detail the direction of pre-to-post changes in each region of (B), and for each food category viewed. Data are shown as mean % change ± SEM. *: p<0.05 for paired t-tests on between-food category responses. #: p<0.05 for one-sample t-tests on responses to each food category against baseline (PRE-intervention session). LPFC: lateral prefrontal cortex. DPFC: dorsal prefrontal cortex. IPL: inferior parietal lobe. PreCG: pre-central gyrus. LF/NSW: Low-Fat/Non-Sweet. LF/SW: Low-Fat/Sweet. HF/NSW: High-Fat/Non-Sweet. HF/SW: High-Fat/Sweet.*

Association between changes in neural source activity to food viewing, body weight and food liking

To complement primary findings on brain responses, we investigated associations between PRE- to POST-intervention changes in neural activity to food viewing, and changes in body weight as well as in food liking using correlation analyses. Participants' body weight at baseline (i.e. PRE-intervention session) ranged from 67-120 kg, corresponding to BMIs ranging from 21.2-35.4 kg/m^2. Changes in body weight from PRE- to POST-intervention sessions ranged from a loss of 3 kg (-3.3% of initial body weight) to a gain of 5 kg (+6.3% of initial body weight).

These changes in body weight were negatively associated with changes in DPFC activity when HF/SW foods had been viewed (ρ_{12}=-0.67; p<0.01). That is, participants who showed higher gains of body weight also showed greater pre- to post-intervention decreases in neural activity when viewing the solid HF/SW foods (Figure 3). No associations between changes in food liking and changes in neural activity were found.

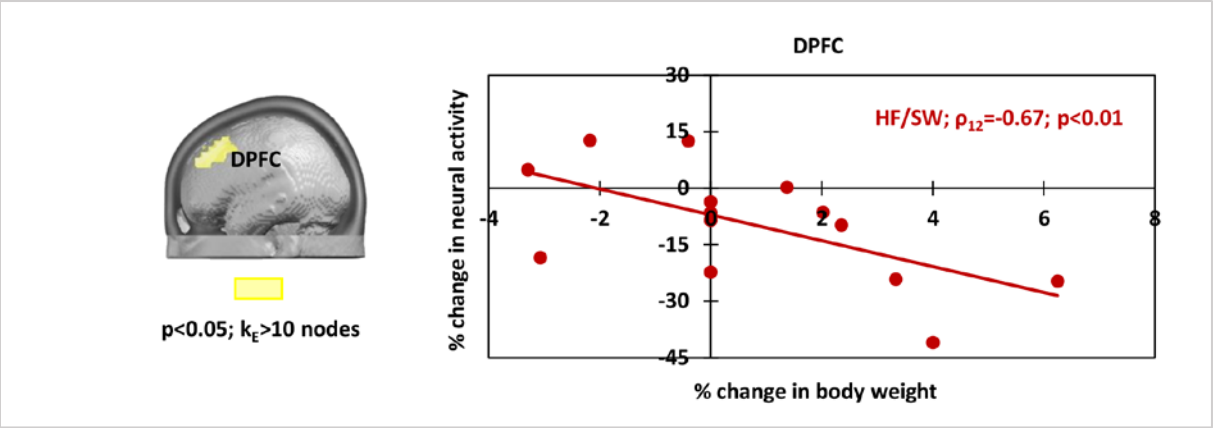

Figure 3: *A negative correlation between changes in body weight and in neural activity to HF/SW food viewing from PRE- to POST-intervention session was obtained in the DPFC over TW1. DPFC: dorsal prefrontal cortex. HF/SW: High-Fat/Sweet.*

DISCUSSION

Our study investigated the effects of a replacement of sugar-sweetened beverages (SSBs) by artificially-sweetened equivalents on brain and behavioral responses to food viewing in intensive SSB consumers. Electrical neuroimaging served to delineate neural sources whose activity was modulated when viewing solid food after the SSB replacement. Although a few EEG studies have been conducted on differential brain responses over nutritional and lifestyle interventions (Murdaugh et al., 2012; Nock et al., 2012; Weygandt et al., 2013; 2015), this study is, to our knowledge, the first one to investigate changes in the spatio-temporal dynamics to food viewing following a sugar-targeting nutritional intervention. The timing of these modulations converges with previous findings (Toepel et al., 2009; Harris et al., 2013). Contrary to our hypotheses, the weight loss over the intervention period was not significant and no pre-to-post changes were observed neither in visual food liking nor in brain responses to palatable food viewing in regions subserving salience and reward attribution. However, neural activity in response to the viewing of high-fat, sweet foods was significantly reduced from pre- to post-intervention in brain regions associated with impulse control. This decrease in activity was associated with weight loss failure, suggesting an impairment in individuals' ability to exert control and adjust their solid food intake during the intervention period.

Decrease in prefrontal activity to palatable food viewing and impairment in cognitive control – Predominantly, a decrease in neural source activity pre-to-post intervention, specifically when high-fat sweet foods were viewed, were found in prefrontal regions. Dorsal prefrontal regions are associated with executive functions such as cognitive control or planning, both in the neurobehavioral science of appetite and object perception in general (Dagher, 2012; Miller, 2000). In particular, dorsal prefrontal functioning is linked to the ability to exert self-control over food intake upon exposure to appetitive food cues (Hare et al., 2009). For example, DelParigi and colleagues (2007) showed stronger dorsal prefrontal activity after meal intake in cognitively restrained eaters as compared to non-restrained individuals, suggesting higher cognitive control, or higher need for control, in restrained eaters (Heatherton & Wagner, 2011). Several similar observations are reported in the review of Rooke and colleagues (2008), who highlight the importance of implicit 'impulse control' for the prevention of substance abuse. In agreement, Batterink and colleagues (2010) showed a negative association between BMI and prefrontal brain activity (both in dorsal and ventro-lateral regions) when adolescent participants were required to inhibit responses to palatable food stimuli. A causal link between the dorsolateral prefrontal cortex and the modulation of valuation processes when viewing palatable foods was established by Camus and colleagues (2009). They used transcranial magnetic stimulation (TMS) to evince the impact of dorsolateral prefrontal cortex on ventral frontal regions at the time of decision-making. Additional ventral and lateral regions of the PFC were found to be involved in cognitive control exertion. For example, Hollman and colleagues (2012) showed that increases in inferior frontal gyrus activity during food response inhibition positively correlated with dietary restraint. Furthermore, Cools and colleagues (2002) showed that ventro-lateral prefrontal cortices promote behavioral inhibition and adaptations. Taken together, these studies highlighted the importance of prefrontal brain areas in control exertion over drives towards palatable foods.

Although few studies have so far investigated longitudinal changes occurring along with nutritional and lifestyle interventions, an increase in dorsal prefrontal activity in response to the viewing of palatable foods has been consistently associated with greater success in weight loss and prevention

of weight (re)gain (Bruce et al., 2011; Murdaugh et al., 2012; Nock et al., 2012; Weygandt et al., 2013; 2015). A study by McCaffery and colleagues (2009) also showed stronger frontal neural activity to high-calorie food image viewing in successful weight-loss maintainers (as defined by lifetime weight history) as compared to their normal-weight and obese counterparts. While an increase in activity in prefrontal regions in response to food cues corroborates with being able to exert cognitive control and lose weight, our results revealed decreased activity in the prefrontal cortex to high-fat sweet foods after the intervention, these changes being associated with weight loss failure (or even weight gain). This failure in weight loss might thus be related to participants' inability to exert cognitive control when faced with highly palatable food items during the diet intervention period, resulting in the increased consumption of such items. Yet, since beverage consumption was not blinded, an alternative explanation of our finding can also be that when consuming the ASB counterpart of their preferred SSB, participants became more inclined to consume more calories from solid foods, i.e. exerting less control over their food intake and preventing weight loss. Since the relation between DPFC activity changes and body weight was only attested via a correlational measure in the present study, future studies are needed to further delineate the general or additional, respectively, impact of non-nutritive sweetener consumption on pre-ingestive brain responses to solid foods cues.

Also, we found intervention-induced modulations as a function of the viewed food category within inferior parietal and precentral gyrus. Neural activity in these regions has been related to attentional (Karhunen et al., 1997) and decision-making processes in the light of subsequent food choices (Kable & Glimcher, 2009). Decreased responses to high-fat and sweet foods during early visual responses have been associated with blunted control mechanisms hindering the down-regulation of attention towards food cues (Harris et al., 2013), in turn increasing motivation toward food intake (Hume et al., 2015). That is, an early decrease in prefrontal cortex activity (as described above) could promote a later increase in attention towards palatable foods. In our study, such pattern can be observed in the precentral gyrus responses. Greater activity in precentral regions has also been found in obese individuals as compared to normal-weight controls and successful weight loss maintainers, which might reflect greater attention towards palatable foods (McCaffery et al., 2009). Altogether, our results likely point out that an imbalance between the exertion of cognitive control and attention towards palatable food cues could promote intake of solid foods over the SSB replacement period due to 'reflexive' eating instead of being a cognitively-driven decision ('reflective'), resulting in weight loss failure (Alonso-Alonso & Pascual-Leone, 2007). Future intervention studies might benefit from a monitoring of daily food choices in parallel to modulations in brain responses to food cues to assess absolute changes in intake behavior and experimental paradigms such as 'go/no-go' tasks specifically investigating impulse control (Carbine et al., 2017) to further corroborate this assumption.

Modulations in food liking and reward valuation processes – Regarding food appreciation ratings (liking of food images), no significant changes were found with respect to baseline pre-intervention for either food category. A similar absence of changes in 'reward' value attribution (assessed both with behavioral tasks and functional magnetic resonance imaging) was observed by Griffioen-Roose and colleagues (2013), who repeatedly exposed participants to ASBs or SSBs. Paralleling behavioral results, no changes were observed from pre- to post-intervention session in brain activity to food viewing in areas associated with reward and salience attribution. We would yet remind the reader

that the online image categorization task performed by participants during EEG recordings (as in Toepel et al., 2009) does not directly assess reward processing.

Some additional limitations regarding the interpretation of our study results should be mentioned. Our design did not include a control group, i.e. participants continuing to consume SSBs over the 3-month intervention period. For this reason, we cannot be certain whether the observed liking and brain responses are specific to the SSB replacement. This protocol was a nested, observational study, and no statistical power analysis was done beforehand. Thus, and as discussed beforehand, it is possible that the sample was too small to detect some differences. Most important is, however, that the current protocol cannot distinguish effects induced by adding artificially-sweetened beverages (ASBs) from those of SSBs removal over the intervention period. In other words, the modulations we observed could well be due to the forced introduction of ASBs to participants' diet, and not necessarily to the cut in SSB consumption. Whether ASB consumption changes the perception of sweet taste has only recently begun to be studied. There is some evidence that chronic ASB consumption might change the way the brain associates sweet taste to high caloric intake, and promotes modulations in intake behavior (Davidson et al., 2011; Franck et al., 2008; Green & Murphy, 2012; Pepino & Bourne, 2011), but results are still not conclusive (Bruyère et al., 2015; Harvey-Anderson et al., 2012; Mattes & Popkin, 2009). Most of these studies used taste stimuli, so that to our knowledge, our study is the first to investigate changes in solid food perception by SSB replacement. Future projects yet also need to explore such changes induced by ASB consumption when novel to the diet.

In conclusion, our study for the first time explored modulations in spatio-temporal brain dynamics to food viewing in the context of a nutritional intervention targeting to reduce sugar intake. Our data provide a valuable starting point for emphasizing the importance of investigating brain responses to food cues occurring in parallel with nutritional intervention, and suggest that a decreased exertion of cognitive control when exposed to palatable food cues, together with functional alterations in brain areas supporting attention, are associated with compensatory intake behaviors and weight loss failure. The absence of other changes such as modulations in liking and in brain areas related to the reward valuation of foods (although potentially explained by the small sample size) further questions the efficiency and relevance of SSB replacement as a sole nutritional intervention. Our study thus highlights the need for implementing multidisciplinary approaches, e.g. providing behavioral training of self-control in daily food intake to dieters (Houben & Jansen, 2011), to render nutritional interventions aiming to decrease body weight successful.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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