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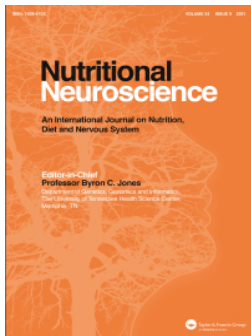
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Human brain responses to the artificial sweetener sucralose and sucrose in the presence of flavour modifier

Hee-kyoung Ko^a, Jingang Shi^b, Thomas Eidenberger^c, Weiyao Shi^b and Ciara McCabe ^a

^aDepartment of Psychology, University of Reading, Reading, UK; ^bEPC Natural Products Co., Ltd., People's Republic of China; ^cUniversity of Applied Sciences Upper Austria, Wels, Austria

ABSTRACT

Objectives: There is a significant need to reduce sugar in food. We can replace sugar with non-nutrient sweeteners; however, they need to be desirable. Previously, we found adding a flavour modifier to a taste can result in neural super-additivity that could drive enhanced pleasure. It is not known if adding a flavour modifier to a non-nutrient sweetener could affect brain activity in the same way.

Methods: Healthy adults ($N = 48$, Mean age 26 yrs.) participated. We examined the neural effects of adding a flavour modifier to the non-nutrient sweetener sucralose (SLM) and the neural effects of sucrose vs sucralose. We examined whole brain data and the ROIs insula, pre- and postcentral gyrus, identified from a meta-analysis on brain responses to sweet tastes.

Results: Super-additive neural effects to SLM were in the mid/inferior temporal gyri, pre- and post-central gyri and parietal areas at the whole-brain level, $p < 0.05$ Family Wise Error corrected threshold. Superior frontal gyrus activity correlated with SLM pleasantness. There were no whole brain differences including reward-related differences between sucrose and sucralose. We did find greater ROI somatosensory activity ($p = 0.01$) for sucrose vs sucralose.

Discussion: We provide the first evidence that adding a flavour modifier to a non-nutrient sweetener reveals synergistic neural activity in brain areas associated with taste sensation, intensity, attention, perception and multisensory integration. Modifiers added to sweeteners could help consumers switch to healthier options and producers reduce the amount of sugar in foods. Future studies should examine if neural super-additivity effects can be used to predict subsequent consummatory behaviour.

KEYWORDS

Neuroimaging; sweeteners; FMP; artificial sweetener; non-nutrient sweetener; sugar; sucrose; brain



Introduction


According to a World Health Organisation report [1] obesity accounted for approximately 5 million deaths in 2019 from noncommunicable diseases (cardiovascular disease, diabetes, cancer, neurological disorders, chronic respiratory diseases and digestive disorders), which corresponded to 12% of all deaths from non-communicable diseases.

The energy imbalance between calories consumed and calories expended is reported as one of the fundamental causes of obesity and being overweight, alongside inactivity [2]. As the global population increases and the intake of energy-dense foods that are high in fat and sugars are increasing, individuals are being called upon to take some responsibility by trying to eat less energy-dense foods and increase their exercise.

However, governments across the world recognise that the food industry can play a significant role in promoting healthy diets that are nutritious, available and affordable to all consumers [3] and one way to do this is to reduce the sugar in processed foods.

This can be achieved by using high intensity non-nutrient sweeteners or non-caloric/low-calorie sweeteners – such as saccharin, sucralose, aspartame, cyclamate, and acesulfame-K in food and beverages [4]. These compounds can attain a given level of sweetness at a much lower concentration than sugar. A recent meta-analysis finds that replacing sugar with non-nutrient sweeteners leads to weight reduction, particularly in participants overweight/obese under an unrestricted diet [5]. Although obesity is linked to reduced sensitivity to sweetness, hormonal changes affecting appetite and an

CONTACT Ciara McCabe  c.mccabe@reading.ac.uk  School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK, RG66ES

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increased craving for sweets, a recent review states that consumption of non-nutrient sweetened foods does not increase sweetness preference or energy intake [6].

Taken together, there is good evidence that non-nutrient sweeteners can be used to reduce calories in foods. However, for food companies to replace sugar with non-nutrient sweeteners there is a real need to develop sugar-like products that have the sweetness and mouthfeel of sugar but without the need for high amounts of sweeteners [7]. One way to do this is to use flavourings with modifying properties (FMPs) to impart and/or mask an intrinsic sensory food profile without adding any new flavour characteristics [8]. Proust 121 (EPC Natural Products Co., Ltd.) is a FMP developed to enhance sweetness and mouthfeel without any perceptual taste or odour itself, tested and approved by FEMA (the Flavour and Extract Manufacturers Association of the United States) [9]. In theory, Proust 121 could be used to enhance the sweetness and mouthfeel of non-nutrient sweeteners to be more sugar-like such that their concentration in foods could be reduced. However, it is unknown how adding flavour modifiers to sweeteners might affect neural activity.

Although we know of no studies examining the neural response to sweeteners combined with a FMP, previous neuroimaging studies have combined sucrose taste with sweet odours and found super-additive neural effects, relative to the sum of the individual components, in regions such as the prefrontal cortex, parietal cortex and insula [10,11].

Therefore, the main aim of this study was to examine if combining a sweetener such as sucralose with the FMP Proust 121 would reveal super-additive neural activity, relative to the sum of the individual components. As the modifier Proust 121 is designed to enhance sweetness this allows the amount of sucralose to be reduced in the combination condition, while keeping the sweetness levels similar across conditions. This allowed us to examine neural effects outside of any perceptual differences in sweetness between when modifier was and wasn't added to the sucralose.

Showing that flavour modifiers enhance neural activity to sweeteners even at low concentrations supports the notion of FMPs to increase the acceptability of non-nutrient sweeteners and aid the reduction of overall sweeteners in foods.

The second aim was to examine the neural response to sucralose vs sucrose given the inconsistencies in the field regards their differential effects on the human brain [12]. Sucralose is considered most similar perceptually to sucrose with no bitter aftertaste compared to other sweeteners [4,13] and

when given at a concentration equally-sweet to 6% sucrose [14] participants find it hard to distinguish them. This allowed us to examine sucralose vs sucrose neural activity outside of any cognitive prejudices related to the tastes.

As sugar is a calorific natural sweetener needed for energy and thus survival it is assumed that it increases neural activity especially in reward regions of the brain more than non-nutrient sweeteners like sucralose. However, despite the paucity of research on basic neural representations of taste and reward responses to simple caloric sweeteners in humans, there have been claims that compared to caloric sweeteners non-caloric sweeteners do not activate the reward system [15]. A recent meta-analysis finds that only two studies with very small sample sizes ($N = 12$, $N = 10$) report increased neural responses to sucrose vs sweeteners [16,17] while others report decreased brain activation to glucose and fructose but not to sucralose [18]. Yeung and Wong conclude that inconsistencies in the field are likely due to small sample sizes and liberal statistical thresholding [19]. A further criticism is that previous studies don't always directly compare the simple differential brain activation between sugar and sweeteners nor do they employ standardized fasting procedures [12].

Therefore, in this study, we recruited what is considered a robust sample size for fMRI ($N = 48$) [20] and employed a standardised fasting and feeding protocol. We examined directly differential whole brain activity between the conditions and report family-wise-error rate (FWE $p < 0.05$)-corrected statistics. We also examined in regions of interest (ROI) analyses, the insula (primary taste cortex) the pre and postcentral gyri as these are most often activated in systematic reviews and metanalysis on sweet tastes [12,15]. We examined the neural super-additive effects of the sucralose plus modifier compared to the sum of sucralose and modifier alone at the whole brain level. We also examined neural effects of sucrose vs sucralose outside of any subjective differences in sweetness. We also added an ROI in the striatum (caudate) as this was reported as different between sucrose and sucralose in [16].

Materials and methods

Participants

Forty-eight healthy and right-handed adults (10 male and 38 female) were recruited for the fMRI study. All participants were between 18 and 45 years old (mean 26.2 ± 6.8) and had a current body mass

index (BMI, weight in kg/height in m^2) or waist-to-height ratio (WTH) in the healthy range. Participants were excluded if they had any current/previous psychiatric history using the Structured Clinical Interview for DSM-IV Axis I Disorder Schedule (SCID), or if they took psychoactive medication, had high depression symptoms (measured with the Beck Depression Inventory (BDI) > 9) [21], or an eating disorder (measured with Eating Attitude Test (EAT) > 20), food allergies, diabetes, smoking, or any contraindications to fMRI scanning. We also recorded the frequency, liking and craving for sugary and sweetened foods [22]. The questions in this scale consisted of 'How frequently do you eat sugary foods?' with answers of either; a few times per month; 1–2 times per week; 3–4 times per week; or more than 5 times per week and 'How frequently do you eat/drink foods with sweeteners?', with answers of either; Never; Rarely; Sometimes; Often; Usually or Always. The Craving and Liking for sugary foods were scored as 1 for low craving and 10 for high craving on a Likert scale. All procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2013 and ethical approval was obtained from the University of Reading Ethics committee, ethics ref: UREC 21/44 all participants provided written informed consent.

Pre-test (Triangle test or taste perception test)

The 48 participants were entered into the study as long as they could distinguish 2% sucrose from a control. This standard taste perception test was as follows: The participants were randomly allocated to the following sequences of two samples A (distilled water) and B (20 g sucrose/litre [2 % Sucrose]): ABB, AAB, ABA, BBA, BAA and BAB. For the individual performance, each participant received all six sequences in random order. In a sequence, the participants took the whole 10 mL of each sample into their mouth, swirled and coated the solution around their mouth for 3 s and then spit it into a spittoon. On each trial after tasting all three, they indicated which was different from the other two. Participants who yielded correct identification of at least 5 out of the 6 trials on a second attempt, were recruited to the study.

Stimuli for the scan (Table 1)

Sucrose (S), sucralose (SL) the flavour modifier Proust (M) and the combination of Sucralose with flavour modifier Proust (SLM) and Sucrose with flavour modifier Proust (SM) provided the basic stimuli set for the

Table 1. Stimuli.

Condition	Abbreviation	Solution
Sucralose + modifier	SLM	6.8 mg sucralose and 36 mg Proust 121
Sucralose	SL	10.5 mg sucralose
Modifier	M	36 mg Proust 121
Sucrose + modifier	SM	4.5 g sucrose and 36 mg Proust 121
Sucrose	S	6 g sucrose
Control	C	25 mM KCl + 2.5 mM NaHCO ₃

fMRI study. The sucrose and sucralose were >99% pure and sourced from Wiener Zucker, Feinkristallzucker, Austria. The flavour modifier (Proust 121, 0.036%) was provided by EPC Natural Products Co., Ltd. As we wanted to keep the stimuli perceptually similar we matched the sucralose concentration (0.0105%) to an equally sweet concentration of sucrose 6% [14] and reduced the sucralose (0.0068%) and the sucrose concentration (4.5%) when combining them with the modifier, as the modifier can increase sweetness [14]. All stimuli were diluted and delivered in distilled water. A tasteless solution (containing the main ionic components of saliva, 25 mM KCl + 2.5 mM NaHCO₃) was used as a control.

The two-alternative forced choice (2AFC) sensory tests were done to verify that the sweetness perception of the low sucralose concentration + modifier was equal to the higher concentration of sucralose alone. To confirm that the modifier does not have a sweet taste of its own we also compared it to 1.5% sucrose, the lowest known concentration of a sweet taste perceivable by humans [23]. Twelve expert sensory panelists recruited from the University of Applied Sciences Upper Austria, were given three times, in a random blinded order, a pair of samples and asked to decide which of the samples tasted more/less sweet. In total $12 \times 3 = 36$ ratings were obtained for each analysis and were statistically evaluated using the beta-binomial evaluation.

Study design

The fMRI scans took place at the Centre of Integrative Neuroscience and Neurodynamics (CINN) at the University of Reading. If scheduled for a morning scan participants fasted overnight, if having an afternoon scan participants fasted for 3 h (no food, only water) before the scan. 11 participants had a morning scan and 37 participants had an afternoon scan. 30 min before scanning all the participants were given a standardized meal similar to previous studies (bagel, cream cheese, banana, orange juice, skim milk, 604 total calories) with the instruction to 'eat until feeling comfortably full, without overeating.' We also asked participants to rate their hunger and mood, before

the scan, on a visual analogue scale from 0 being not at all to 10 indicating the most ever felt. Subjects were screened for potential pregnancy and metal in their body before being placed in the fMRI scanner.

The task had an event-related interleaved design, to reduce carry over taste effects between trials [24] and delivered in random permuted sequence the following five stimuli, [Sucrose, S], [Sucralose, SL], [Modifier, M], [Sucrose + Modifier, SM], [Sucralose + Modifier, SLM]. The number of stimuli was chosen to be feasible given the number of repetitions of each stimulus (10) and the length of time that subjects were in the magnet. Tastes were delivered to the subject via separate long (~3 m) thin Teflon tubes with a mouthpiece (~1 cm in diameter) at one end, that was held by the subject comfortably between the centre of the lips. At the other end the tubes were connected to separate reservoirs via syringes and one-way Syringe Activated Dual Check Valves (Model 14044-5, World Precision Instruments, Inc) which allowed any stimulus to be delivered manually by the researcher at exactly the right time indicated by the programme [25] thus avoiding the delays and technical issues experienced when we have used computerised syringe drivers.

fMRI task

Similar to our previous taste studies at the beginning of a trial, a green cross at the centre of the screen indicated the start of the trial for 2 s. Then, one of the five stimuli was delivered in a 0.5 mL aliquot to the subject's mouth, the word taste was presented at the same time on the visual display. The instruction given to the subject was to move the tongue once as soon as a stimulus was delivered in order to distribute the solution round the mouth to activate receptors, and then to keep still for the remainder of the 5 s taste period until 'Swallow' was shown, when the subject could swallow. Swallowing was 2 s, then the subject rated 'pleasantness', 'wanting', (+2 to -2) and 'fullness' (0 to +4) on a visual analogue scale by moving a bar to the appropriate point on the scale using a button box, ratings similar to those used in previous taste/fMRI studies [26]. Each rating period was 5 s long. After the last rating on each trial the tasteless control solution was administered in the same way as the other stimuli and was used as the comparison condition to allow somatosensory effects produced by liquid in the mouth, and the single tongue movement made to distribute the liquid throughout the mouth, to be controlled for [10,27]. The tasteless control condition was not subjectively rated. Then, a red cross was presented for a duration between 0.8 and 2

s (jittered) to indicate the end of the trial. After the red cross, the screen was black for 2 s before a new trial started. A taste trial was repeated for each of the five stimuli, and the whole cycle was repeated 10 times, resulting in 50 trials ~33 s long giving a total task time of ~27.5 min.

fMRI data acquisition

Images were acquired with an event-related interleaved design and Siemens Magnetom Trio 3 T whole-body MRI scanner and a 32-channel head coil (Siemens Healthcare, Erlangen, Germany) at the Centre for Integrative Neuroscience and Neurodynamics at the University of Reading. T2*-weighted echo planner imaging slices (TE 30 ms) are obtained every 2.160 s (repetition time, TR). The matrix size was 64 mm and the field of view was 192 mm. 40 axial slices with in-plane resolution of 3 × 3 mm and between-plane spacing of 3 mm are obtained. An anatomical T1 volume with sagittal plane slice thickness of 0.9 mm and in-plane resolution of 0.9 × 0.9 mm will also be acquired.

fMRI data analysis

The imaging data were analysed using SPM12 (Wellcome Centre for Human Neuroimaging, University College London). Pre-processing of the data used SPM12 realignment, slice timing, coregister, segment, normalization to the MNI coordinate system (Montreal Neurological Institute; [28]), and spatial smoothing with 8 mm full width at half maximum isotropic Gaussian kernel. The time series at each voxel was low-pass filtered with a haemodynamic response kernel. Time series non-sphericity at each voxel was estimated and corrected for, with a high-pass filter with cut-off period of 128 s.

In the single-event design, a general linear model was then applied to the time course of activation in which stimulus onsets were modelled as single impulse response functions and then convolved with the canonical hemodynamic response function. Linear contrasts were defined to test specific effects. Following smoothness estimation, linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual data-set. Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic (transformed into the unit normal distribution (SPM z)). Movement parameters were added as additional regressors.

We then examined the direct comparison of [sucrose] vs [control], [sucralose] vs [control], [modifier] vs [control], [sucrose] vs [sucralose] and

[sucralose + modifier] vs [sucralose] and if areas were more strongly activated by the combination [sucralose + modifier] than by the sum of any activations produced by the two stimuli presented separately e.g. SLM > Sum (SL, M) in the whole brain, similar to previous studies [22,29]. We also examined regions of interest such as the insula (primary taste cortex) and precentral and postcentral gyrus (somatosensory regions) given these are most often reported in systematic reviews and metaanalysis on sweet tastes [12,15]. Spheres (10 mm) were created from coordinates identified in the meta-analysis on sweet tastes in humans [anterior insula: -32, 16, 2; posterior insula: -38, -2, -12] precentral [58 2 24] postcentral [60 -16 24] [15] using WFU pickatlas, for the caudate ROI we used the aal anatomical atlas in WFU pickatlas. Data were extracted using the SPM ROI analysis Matlab code and SPM's `spm_get_data` command and analysed with paired-sample *t* tests in excel. Similar to previous studies on sucrose vs sucralose [16,17] we also report whole brain data. We thresholded at $p < 0.05$ corrected (familywise-error (FWE)) and *p*-values cluster corrected at both $p < 0.05$ False Discovery Rate (FDR) and $p < 0.05$ FWE. We also checked if the results were affected by gender, hunger level and scan time (morning or afternoon) added as covariates of no interest.

We also did exploratory analysis examining the relationship between whole brain neural activity and the subjective ratings (pleasantness, wanting and fullness) across all participants using a multiple regression analysis in SPM12. As there was very little variability in the subjective ratings, (as we designed the study to make it difficult for participants to distinguish between stimuli) we used a lenient threshold of $p = 0.05$ uncorrected. For example, all participants' scans for the condition sucralose were entered into a model as a regressor with the corresponding participant's subjective pleasantness ratings added as an additional regressor. This allowed us to run correlations between neural activity and ratings.

Results

Sensory results

Examining data from twelve sensory panelists, (mean 24yrs, SD, 2.91) 9 female and 3 male with healthy weight (BMI mean 24.7, SD, 5.35) and mood (BDI mean 5.87, SD, 3.24) and eating attitudes (EAT mean 4.92, SD, 2.14). A beta-binomial analysis including the 3 replicate testing for each panel member was performed and the *p*-value refers to the beta-binomial test design [9]. We found no statistical difference in

Table 2. Sensory Data: Sweetness Equivalence (more/less sweet).

Replicate 1	Replicate 2	Replicate 3	Sum	<i>p</i> -value
Sucralose (SL) 0.0105% vs Sucrose (S) 6%				
5/7	7/5	4/8	16/20	0.319
Sucralose (SL) 0.0068% plus Proust 121 (M) vs. Sucralose (SL) 0.0105%				
8/4	5/7	7/5	20/16	0.319
Proust 121 (M) vs. Sucrose (S) 1.5%,				
5/7	3/9	1/11	9/27	0.001

In a random blinded order participants rated a pair of samples and asked to decide which of the samples tasted more/less sweet.

sweetness equivalence of the conditions sucralose 0.0105% and sucrose 6% (Table 2).

When examining the sweetness equivalence of the mixture of sucralose 0.0068% plus the modifier Proust 121 vs. sucralose alone 0.0105% the results show no statistical difference between the two samples for sweetness (Table 2).

When examining the sweetness equivalence of Proust 121 vs. sucrose 1.5%, Proust 121 was shown to be significantly less sweet than a 1.5% sucrose solution which is considered the lowest perceivable concentration of a sweet taste for humans [23]. Indicating that Proust on its own has no perceptible sweetness, as expected (Table 2).

Demographic data for fMRI study

48 participants took part in the fMRI part with a mean age of 26 yrs. 38 were female and 10 male. All were in the healthy BMI or weight to height ratio [30] range and had scores in the healthy range for mood (BDI <9) and eating attitudes (EAT <20). Participants also rated their craving and liking for sugary foods out of a maximum score of 10 and their frequency of eating sugary foods and foods with sweeteners out of a maximum score of 5 (see Table 3).

Pre-test results of sensitivity to 2% sucrose

Twenty-seven participants passed the pre-test with 6 out of 6 trials correct first time. Sixteen participants passed the pre-test with 5 out of 6 trials correct first

Table 3. Demographics.

	All (n = 48) Mean score (SD)
Age, years	26.26 (6.8)
Gender, female/male: <i>n</i>	38/10
Body mass index	22.67 (2.7)
BDI	3.42 (2.7)
EAT	3.15 (3.1)
Craving for sugary foods	5.52 (1.8)
Liking for sugary foods	6.46 (2.2)
Freq eating sugary foods	2.77 (1.6)
Freq eating/drinking foods with sweeteners	1.98 (1.3)

Table 4. Visual analogue Scale.

	Mean score (\pm SD)
Appetite	
How hungry do you feel right now?	2.14 \pm 1.91
How full do you feel right now?	6.87 \pm 1.94
Mood	
Alertness	6.50 \pm 2.10
Disgust	0.37 \pm 0.60
Drowsiness	2.25 \pm 2.13
Anxiety	1.79 \pm 1.55
Happiness	6.68 \pm 1.22
Nausea	0.33 \pm 0.66
Sadness	0.85 \pm 1.50
Withdrawn	0.87 \pm 1.29
Faint	0.20 \pm 0.50

Rate between 0 and 10, where 0 = Not at all, 10 = Most ever felt

time and five participants got 6 of the 6 trials correct on their second attempt, so were also included in the study.

fMRI scan day

Subjective hunger and mood

Participants had relatively high mood and low hunger levels before the scan (Table 4).

Subjective ratings of stimuli: pleasantness, wanting and fullness ratings during the scan

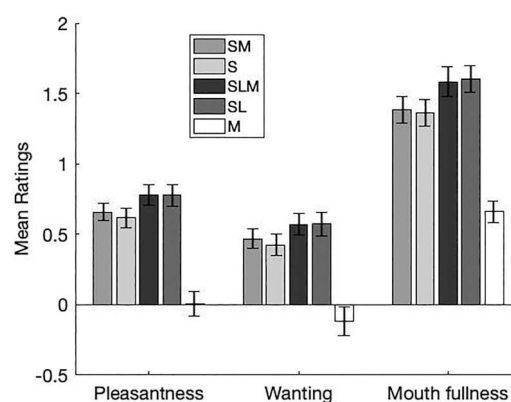
Using repeated measures ANOVA with ratings made during the scans (3 levels, pleasantness, wanting, mouth fullness) as one within subject factor and condition (4 levels, SL, SLM, S, SM) as a second within subject factor. We found a main effect of ratings ($F = 107$ (1.13, 53.18) $p < 0.001$) and a main effect of condition ($F = 11.01$ (2.15, 101.25) $p < 0.001$), but no ratings * condition interaction ($F = 1.55$ (3.11, 146.33) $p = 0.20$).

Follow up paired sample t-tests revealed significant increased pleasantness for SLM vs SM ($t = -2.76$, $p = 0.008$), for SL vs SM ($t = -2.419$, $p = 0.020$), SLM vs S ($t = 3.68$, $p = 0.001$) and SL vs S ($t = 2.97$, $p = 0.005$). There was also significantly increased wanting for SLM vs S ($t = 2.63$, $p = 0.01$), SL vs S ($t = 2.26$, $p = 0.02$), and mouth fullness was increased for SLM vs SM ($t = -3.78$, $p < 0.001$), SL vs SM ($t = -4.57$, $p < 0.001$), SLM vs S ($t = 3.93$, $p < 0.001$), SL vs S ($t = 4.53$, $p < 0.001$) (Figure 1).

Whole brain analyses

Main effects of taste stimuli

The sucrose, sucralose and modifier activated regions such as the primary taste cortex (insula), primary somatosensory cortex (postcentral gyrus), and the

**Figure 1.** Subjective ratings made in scanner.

precentral gyrus and caudate (Table 5). Sucrose vs control condition also activated the hippocampus, the superior temporal gyrus (STG) and the Rolandic operculum.

Super-additivity: SLM > Sum (SL, M)

To examine any super-additive effects of combining the modifier with the sucralose i.e. is there more activity to the combination than to the sum of the parts, even when sweetness is controlled, we used the contrast SLM > Sum (SL, M). We found activity in regions similar to that of the individual tastes alone such as the pre and post central gyri. However, the parietal cortex and the mid/inferior temporal gyri (Figure 2) were also activated (Table 6). Similarly, when adding the flavour modifier to sucrose there was super-additivity activity in pre and post cingulate gyri, regions activated by the tastes alone but also in the parietal cortex and inferior temporal gyrus (Table 7).

S vs SL, SLM vs SL

Whole brain direct comparisons of sucrose vs sucralose and sucralose plus modifier vs sucralose (matched for sweetness) revealed no significant differences, thresholded at $p < 0.05$ FWE corrected.

ROI analyses:

S vs SL, SLM vs SL, SM vs S

We found greater neural activity in the sucrose condition vs the sucralose condition in the insula [38 -2 -12], $p = 0.04$, the precentral gyrus [58 2 24], $p = 0.05$ and the postcentral gyrus [60 -16 24], $p = 0.01$ (Figure 3). We also found greater neural activity in the sucralose plus modifier condition vs the

Table 5. Main effects of tastes.

Region	Coordinate	Z-score	No of voxels	<i>p</i> FWE	<i>p</i> FDR
Sucrose-control					
Postcentral gyrus	−42 −22 53	7.17	2916	<0.0001	<0.0001
Precentral gyrus	−57 5 29	6.82			
Supplementary Motor Area	−6 11 50	6.49			
Caudate	9 17 2	6.33			
Anterior Insula	−33 20 −1	5.62			
Hippocampus edge	42 −16 −13	5.98	69	<0.0001	=0.029
Superior Temporal gyrus	−45 −16 −13	5.30	144	<0.0001	=0.002
Rolandic Operculum	39 −4 11	5.10	30	=0.003	=0.189
Superior Occipital gyrus	−15 −94 29	5.09	18	=0.006	=0.351
Region	Coordinate	Z-score	No of voxels	<i>p</i> FWE	<i>p</i> FDR
Sucralose-control					
Threshold: <i>p</i> = 0.05 FWE corrected					
Postcentral gyrus	−42 −22 50	6.19	590	<0.0001	<0.0001
Precentral gyrus	−30 −16 53	5.97			
Precentral gyrus	−57 2 29	4.85			
Caudate	12 17 5	5.68	333	<0.0001	<0.0001
Caudate	−9 17 2	5.18			
Anterior Insula	−27 23 2	4.89			
Supplementary Motor Area	−3 5 62	5.12	114	<0.0001	=0.005
Supplementary Motor Area	3 8 59	5.10	228	<0.0001	<0.0001
Postcentral gyrus	60 5 38	5.42	92	<0.0001	=0.008
Region	Coordinate	Z-score	No of voxels	<i>p</i> FWE	<i>p</i> FDR
Modifier-control					
Threshold: <i>p</i> = 0.05 FWE corrected					
Postcentral gyrus	−42 −22 53	7.09	754	<0.0001	<0.0001
Precentral gyrus	−42 2 35	5.60			
Anterior Insula	−30 20 −4	6.87	777	<0.0001	<0.0001
Caudate	12 17 2	6.51			
Caudate	−12 17 2	6.49			
Supplementary Motor Area	−3 14 56	6.60	400	<0.0001	<0.0001
Inferior Frontal gyrus	45 26 23	5.26	96	<0.0001	=0.009
Postcentral gyrus	66 −4 35	5.59	108	<0.0001	=0.007
Mid Cingulate gyrus	0 −22 32	4.91	28	=0.004	=0.158
Inferior Parietal cortex	−33 −52 41	4.78	26	=0.005	=0.158

Threshold: *p* = 0.05 FWE corrected.

sucralose alone condition in the precentral gyrus [58 2 24], *p* = 0.03 and for the sucrose plus modifier condition vs sucrose alone [−38 −2 −12], *p* = 0.04. We found no significant differences for S vs SL, SLM vs SL, SM vs S in the caudate ROI. When correcting for multiple comparisons only the sucrose vs sucralose postcentral gyrus activity remained significant (*p* = 0.05/4 ROIs) (Figure 3).

Parametric modulation

When examining correlations between the conditions and the subjective ratings at the level of the whole brain we found a positive correlation between the superior frontal gyrus region for the sucralose plus modifier condition and pleasantness ratings [−21 20 35], *p* < 0.0001, *z* = 3.88 (Figure 4) and wanting ratings [−21 −10 35], *p* < 0.004, *z* = 4.4.

We also examined correlations between the conditions and the subjective ratings in the ROIs. We found positive correlations between the sucralose plus modifier condition and wanting ratings in the

left caudate ($\rho_1 = 0.25$, *p* = 0.04, one-tailed), and between the sucrose plus modifier condition and fullness ratings in the right caudate ($\rho_1 = 0.27$, *p* = 0.03, one-tailed), and between sucralose and wanting ratings in the right posterior insula ($\rho_1 = 0.26$, *p* = 0.03, one-tailed), however these did not survive corrections for multiple comparisons (*p* = 0.05/5 ROI).

Discussion

This is the first study to examine the neural effects of adding a modifier to a sweetener like sucralose. In support of our hypothesis, we found synergistic neural activity in the mid/inferior temporal gyri, the pre and postcentral gyri and the occipital and parietal regions for sucralose combined with the modifier compared to the sum of the activation to sucralose alone and the modifier alone. We also found the superior frontal gyrus (SFG) activity tracked the increasing pleasantness and wanting for the sucralose plus modifier condition.

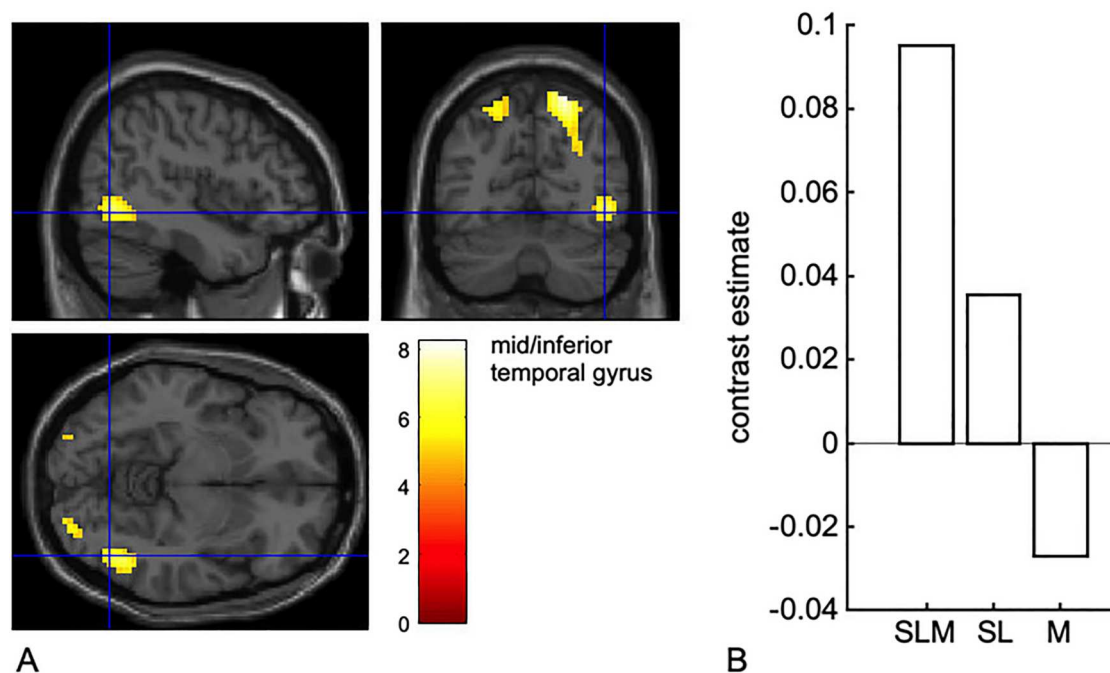


Figure 2. A. SLM > Sum (SL, M) in mid/inferior temporal gyrus [45, -67, -4] $z = 5.7$ $p < 0.001$ FWE cluster corrected (Thresholded at $p < 0.05$ FWE whole brain corrected). B. Contrast Estimates extracted from ITG for SLM, SL and M separately, visualisation of data only, no inferential statistics, hence no error bars.

Table 6. SLM > Sum (SL, M).

Region	Coordinate	Z-score	No of voxels	p FWE	p FDR
Superior Parietal cortex	21 -64 59	6.44	294	<0.0001	=0.001
Mid/Inf Temporal gyrus	45 -67 -4	5.70	107	<0.0001	=0.020
Postcentral gyrus	-42 -25 59	5.01	38	=0.004	=0.138
Precentral gyrus	-33 -22 68	4.76			
Superior Parietal	-24 -61 56	5.16	83	=0.001	=0.032
Mid Occipital gyrus	-27 -91 -1	4.74	25	=0.008	=0.209

Threshold: $p = 0.05$ FWE corrected.

The temporal gyri, pre and post central gyri and parietal areas have all been identified in meta-analyses of brain responses to sweet tastes [15]. The mid/inferior temporal gyri have been implicated previously in taste sensation and taste intensity [31] while the parietal lobe plays a role in sensory perception and integration and managing senses including

taste and smell [32]. The superior parietal lobe has close links with the occipital lobe and is involved in aspects of attention and visuospatial perception, including the representation and manipulation of objects [32].

The SFG is thought to contribute to higher cognitive functions [33] and has subregions involved in cognitive and motor control, cognitive execution and attention and memory processing [34] and has been found previously activated to subjective pleasantness [35].

Taken together, neural super-additivity to sweeteners combined with modifiers in taste sensation [15] and taste intensity areas [31,32] and correlations with pleasantness in the SFG supports the idea that modifiers could enhance the consumer experience of sweeteners thus helping replace sugar in desirable foods.

Table 7. SM > Sum (S, M).

Region	Coordinate	Z-score	No of voxels	p FWE	p FDR
Superior Parietal	21 -67 62	7.09	331	<0.0001	<0.0001
Superior Parietal	-21 -61 53	5.46	108	<0.0001	=0.009
Inferior Temporal gyrus	45 -61 -7	5.45	85	<0.0001	=0.016
Precentral gyrus	-33 -19 68	5.27	63	=0.001	=0.031
Postcentral gyrus	-39 -25 59	5.12			
Mid Occipital gyrus	-27 -94 -4	5.21	26	=0.005	=0.158

Threshold: $p = 0.05$ FWE corrected.

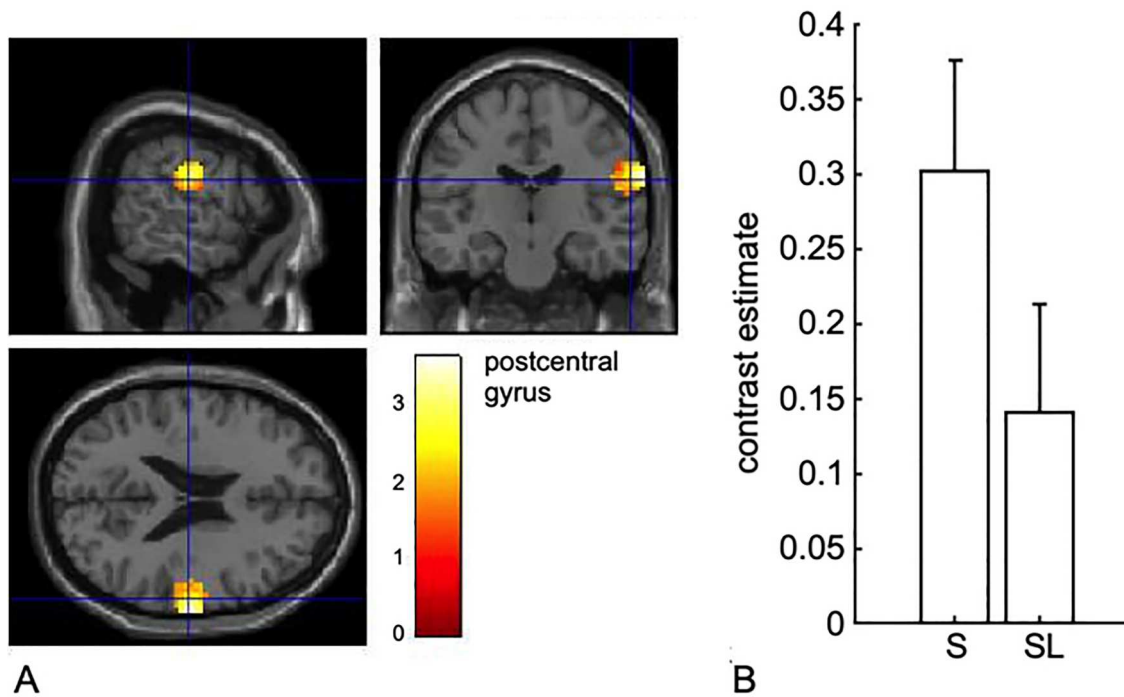


Figure 3. A. Image from the Sucrose (S) vs Sucralose (SL) ROI postcentral gyrus [60 –16 24] B. Contrast Estimates extracted from postcentral gyrus for S and SL separately using SPM get data, t-test $p = 0.015$, bars = standard error.

Future studies should examine if the neural activity shown here can be used to predict subsequent consummatory behaviour, thus extending further our understanding of how sweeteners plus modifiers could be used to replace sugar in desirable foods.

Another aim was to examine how sucrose might differ from sucralose at the neural level. Overall the findings in the literature are inconsistent and a recent

meta-analysis suggests this is likely due to small sample sizes ($N = 10$) and lenient statistical thresholding [12]. Yet with these methods improved we found no differences between sucrose and sucralose at the whole brain neural level. Further we examined the caudate as this was a striatal region found previously different between sucrose and sucralose [16] however with an anatomical ROI for the caudate we found no

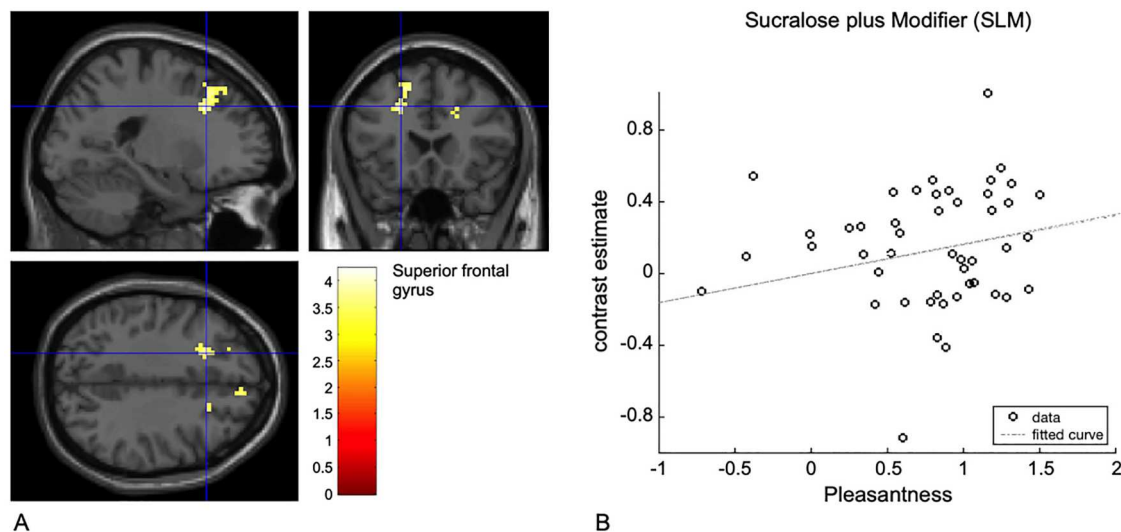


Figure 4. A. Parametric modulation between SLM condition and Pleasantness reveals SFG activation [–21,20,35], $p < 0.001$, $z = 3.88$, FWE cluster corrected (*Thresholded at 0.05 uncorrected*) B. Estimates extracted from SFG cluster using SPM get data function and plotted against pleasantness ratings, for visualisation only.

differences between sucrose and sucralose. This is consistent with previous studies that also find no differences between sucrose and sweeteners including no differences in reward-related areas of the brain [12,15,18].

The ROI analysis revealed increased postcentral gyrus activity for sucrose vs sucralose which could reflect an 'objective' sensing of sweetness from sucrose as the postcentral gyrus has been found previously activated by sweet tastes [12] and is part of the somatosensory cortex [36] and is modulated by sweet taste intensity [37].

Finally although sucrose is considered a pure taste and non-volatile previous studies report that even non-volatile tastants might be being smelled retro-nasally during food oral processing and before swallowing [38]. Therefore, we were curious to explore the sucrose vs control condition for any olfactory activity that could suggest retro-nasal processing. We found the hippocampus, the superior temporal gyrus (STG) and the Rolandic operculum activated. The hippocampus has been shown in mice to be involved in taste and nutrient sensing [39] and it innervates the nucleus accumbens shell, a reward region, that modulates sugar feeding [40]. Also the superior temporal gyrus is considered a primary sensory region of the brain that is involved in taste perception [41] evidenced by temporal lobe lesion studies [42] and consistent with this has been reported as a region activated by sweet tastes in a recent meta-analysis [15]. The Rolandic operculum however is a region that plays a central role in flavour perception and is described as a primary site of olfactory – gustatory integration [43,44]. This finding could reflect oral somatosensory processing as seen in previous studies on sucrose [45] or imply retro-nasal processing, further studies on retro-nasal responses to pure tastes such as sucrose are needed to clarify this.

Strengths, limitations, and implications:

The strengths of the study include using a robust sample size ($N = 48$), a standardised fasting and feeding protocol, and direct neural comparisons of conditions with strict statistical thresholding also. Most participants were female however, which is a limitation that should be addressed in future studies. Together, this work implies that directly combining sucralose with a modifier can lead to synergistic neural activity, in line with our hypothesis. Super-additive affects in brain areas associated with taste sensation, intensity, attention, perception, and multi-sensory integration as shown here could underpin

potential mechanisms by which non-nutrient sweeteners could be made more acceptable in diets, thus aiding sugar replacement. Future studies should examine if neural super-additivity effects can be used to predict subsequent consummatory behaviour.

Author contributions

CMcC, TE, JS, WS conceived and designed research. JS, WS and TE prepared and supplied the study samples. HK and TE conducted research and analysed the data supported by CMcC. CMcC and HK drafted the article. All authors actively participated in editing and reviewing the manuscript.

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Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interest.

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Weiyao Shi and Jingang Shi are employees of EPC Natural Products Co., Ltd who provided the compounds and funded the study. The work was conducted independently at the NRG laboratory of Prof. McCabe at the University of Reading solely for the purpose of scientific understanding. All authors declare that they have no other known competing financial interests or personal relationships that could have appeared to influence the findings reported in this paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [CMcC], upon reasonable request.

Notes on contributors

Dr Hee-kyoung Ko is a neuroscientist who did her PhD at Boston University (USA) on the role of fixational eye movements in high-acuity tasks using an eye-tracker (psychophysical studies). She then completed post-doctoral positions at John Hopkins University, USA and The University of Texas (Austin), USA. More recently, she worked as a research scientist at the University of Oxford (UK),

Department of Physiology, Anatomy and Genetics, linking neuronal responses to visual perception and decision-making using electrophysiological recording. In recent projects, at the University of Reading, UK, she examined the subjective perception and neural response to sweet food tastes in humans and the effect of retro-nasal olfaction on sugar and sweetener tastes using fMRI. She is interested in functional connectivity between perceptual decision-making and reward systems in the human brain and the prediction of behaviour.

Jingang Shi is a pioneering expert in natural sweeteners, best known for driving the global adoption of stevia as co-founder and Chairman of Sweet Green Fields, later acquired by Tate & Lyle. He holds a Master's in Chemical Engineering and an EMBA. Jingang's research has broken new ground in sensory science, particularly through his hypothesis that taste stimuli can be perceived via retronasal olfaction. His investigations into the neural pathways and mechanisms of retronasal perception have provided important insights into how these processes influence flavor perception in food and beverages. His findings have been published in respected journals, including *Chemical Senses* and *Food Quality and Preference*. Jingang now serves as a scientific consultant to a top global beverage company, advising on sugar reduction and sensory research. Currently, he serves as Chief Innovation Officer at EPC Natural Products Co., Ltd..

Thomas Eidenberger is a Professor of Analytical Chemistry, Food- and Bio-technology at the University of Applied Sciences in Upper Austria. He is the former Head and Owner of Belan ZT-GmbH, an accredited testing facility for food with authorization to issue Expert Opinions according to § 73 LMSVG (conformity statements for adherence to EU food regulations). He developed a series of innovative food ingredients, especially natural colorants and sweeteners. His research interests are sensory analysis of food and phytochemistry, including testing physiological (in-vitro and in-vivo) but also technological properties. He is an inventor in more than 30 patents and published more than 20 peer-reviewed articles.

Weyao Shi earned her Bachelor's degree in Chemical Engineering from Lehigh University and a Master's degree in Management of Innovation and Technology from New York University. She currently serves as Director of Innovation at EPC Natural Products Co., Ltd., where she leads scientific research initiatives focused on the development of novel food ingredients and sensory science. Weyao is a co-inventor on more than ten patents pertaining to innovative food technologies and a co-author of several peer-reviewed publications investigating the generation of food aerosols in the oral cavity, their retronasal transport, and subsequent neural perception mechanisms.

Ciara McCabe is a Professor of Neuroscience, Psychopharmacology and Neuroscience in the Psychology Department at the University of Reading, UK. She is also the Director of the Neuroscience of Reward Group at Reading University. Professor McCabe has won many academic awards in relation to her work on the neurobiological basis of reward function in health and disease. She is interested in neuropsychiatric disorders such as depression, and particularly the

symptoms of anhedonia. She examines reward functions using primary (food rewards, social rewards) and secondary rewards (money). She is also interested in the effects of nutritional and psychopharmacological challenges on the neural reward response. Professor McCabe has published over 70 peer-reviewed articles and book chapters and has a H-index of 33, with over 4500 citations.

ORCID

Ciara McCabe  <http://orcid.org/0000-0001-8704-3473>

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