# Brain processing: sugar and sweeteners

This entry aimed to reveal the differential brain processing of sugars and sweeteners in humans. Functional magnetic resonance imaging studies published up to 2019 were retrieved from two databases and were included into the review if they evaluated the effects of both sugars and sweeteners on the subjects' brain responses, during tasting and right after ingestion. Twenty studies fulfilled the inclusion criteria. The number of participants per study ranged from 5 to 42, with a total number of study participants at 396. Seven studies recruited both males and females, 7 were all-female and 6 were all-male. There was no consistent pattern showing that sugar or sweeteners elicited larger brain responses. Commonly involved brain regions were insula/operculum, cingulate and striatum, brainstem, hypothalamus and the ventral tegmental area. Future studies, therefore, should recruit a larger sample size, adopt a standardized fasting duration (preferably 12 h overnight, which is the most common practice and brain responses are larger in the state of hunger), and reported results with familywise-error rate (FWE)-corrected statistics. Every study should report the differential brain activation between sugar and non-nutritive sweetener conditions regardless of the complexity of their experiment design. These measures would enable a meta-analysis, pooling data across studies in a meaningful manner.

## 1. Introduction

Non-nutritive sweeteners were invented as sugar substitutes without calories or with lower calories. With the reduced calorie content, non-nutritive sweeteners should be beneficial to the health of patients with obesity or diabetes mellitus. However, there were conflicting pieces of evidence with regards to how non-nutritive sweeteners affect eating behavior and health.

On the positive side, meta-analyses of human randomized clinical trials have shown that the use of non-nutritive sweeteners could lead to reduced energy intake and body weight [1][2]. On the negative side, exactly the opposite was found in children from epidemiologic studies [3]. Another meta-analysis concluded that sodas sweetened with non-nutritive sweeteners led to an increased risk of obesity compared to sodas sweetened by sugars [4]. One possible explanation for this is that the use of non-nutritive sweeteners induced compositional and functional changes to the intestinal microbiota and hence led to the development of glucose intolerance [5]. However, randomized controlled trials in specific population groups, such as those during gestation, infancy and childhood, were very limited [6]. In addition, observational studies and clinical trials that probed into the underlying physiological effects of non-nutritive sweeteners such as glucose metabolism and appetite-regulating hormones were largely heterogeneous in the study designs, resulting in huge confounders [7]. Moreover, an association between the use of non-nutritive sweeteners and increase in body weight was not observed in observational or animal studies [8].

The unfavorable health outcomes potentially brought on by non-nutritive sweeteners other than weight gain and obesity were also investigated by the literature, such as headaches, depression, behavioral and cognitive effects, cancer, dental caries, diabetes, preterm delivery, and cardiovascular effects [9]. All were without conclusive evidence [9].

The food intake or energy intake behavior is crucial for reducing calorie intake and thus managing weight issue or metabolic syndromes. It was previously demonstrated that humans could sense calorie differences in foods with equal sweetness [10]. The AMP-activated protein kinase was described as a key energy sensor that could modulate the signaling pathways of SIRT1, Ulk1, and mTOR [11]. It is still largely unknown how these signaling pathways relate to the eventual brain responses, but it was reasoned that calorie sensing would eventually be modulated by cerebral processing. Therefore, it would be reasonable to deduce that non-nutritive sweetener and sugar should cause differential activation in the brain, as the former had no or very low calorie content, whereas the latter had a high-calorie content. Understanding the differences in brain response should help researchers and clinicians devise more precise strategies to control the weight of concerned patients, especially concerning the sensitization (increased response) and habituation (reduced response) effects of repeated exposure to the stimuli. However, to the best of the author's knowledge, there has been no

systematic review into differential brain processing of sugars and sweeteners in humans. This systematic review, therefore, aimed to bridge this gap and reveal whether there existed consistent evidence of differential brain processing between the two.

## 2. Discussion

### 2.1. Differential Brain Responses During Tasting

Three studies have reported larger brain responses elicited by sugars than sweeteners among the generally healthy subjects, such as in the insula/operculum [12][13][14], cingulate [15][16], striatum [15], orbitofrontal cortex [17], superior frontal gyrus [15], and precentral gyrus [16]. No study reported vice versa for generally healthy subjects. One study reported no significant difference between sugars and sweeteners [18].

For specific subject groups, the involved brain regions were different. For patients recovered from bulimia, sugars elicited larger responses than sweeteners in the insula/operculum and striatum [19]. Besides, two studies reported sweeteners triggering larger responses than sugars, namely the orbitofrontal cortex among non-diet soda drinkers [20], and the insula/operculum and striatum among patients recovered from anorexia [19].

Repeated exposure to sugars and sweeteners could affect the brain responses, as the brain would be sensitized to the stimuli. The extent of the sensitization was different between the two. Among the healthy subjects and patients recovered from bulimia, the increase in the response level to sugars was larger than sweeteners in the striatum and precuneus [16][21], cingulate, thalamus, and cerebellum [21] In contrast, the increase in the response level to sweeteners was larger than sugars in these brain regions among patients recovered from anorexia [21].

One study reported an interaction between stimulus type and appetite [18]. Several brain regions responded differentially between sugars and sweeteners in hungry and satiated conditions, including the insula/operculum, cingulate, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, precentral gyrus, postcentral gyrus, thalamus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, and inferior parietal gyrus [18]. Haase *et al.* [22] did reported the differential responses between hungry and satiated conditions, but with sugars and sweeteners considered separately, so there were no directly comparable results.

Four studies reported results from sugars and sweeteners separately [23][24]. Two of them concluded that sugars elicited responses in more brain regions than sweeteners. Chambers *et al.* [23] reported that both activated the insula/operculum and dorsolateral prefrontal cortex, with sugars additionally activated the striatum and cingulate. Meanwhile, Haase *et al.* [22] reported that both activated the striatum, thalamus, cuneus, parahippocampus, and hippocampus. Sugars additionally activated the insula/operculum, cingulate, amygdala, orbitofrontal cortex, middle frontal gyrus, medial frontal gyrus, postcentral gyrus, ventral tegmental area/substantia nigra, hypothalamus, superior temporal gyrus, fusiform gyrus, precuneus, cerebellum, and angular gyrus. Sweeteners did not activate these brain regions, but the precentral gyrus and lingual gyrus instead.

The most common brain regions reported in the above studies seemed to be the insula/operculum (7 studies), cingulate (7), and striatum (6). They were frequently reported in meta-analyses of food and taste neuroimaging studies as the core structures of a taste processing network [25][26], and especially for processing the hedonic values of food [26]. Indeed, when viewing high-caloric food pictures, women with obesity had a higher activity level in the striatum than women with normal-weight, and the activity levels of striatum, insula, and cingulate were positively correlated to the body mass index [27]. The phenomenon of higher activation in the group with obesity was also observed in men, even after eating [28]. Moreover, the activity level of the cingulate and striatum reduced in response to high-caloric food pictures after gastric bypass surgery to control obesity [29]. The differential activations of these brain regions by sugars and sweeteners offered a glimpse into the underlying different neural processing of them. However, there was no clear consensus whether sugars or sweeteners elicited larger responses in the brain, though results tended to suggest that the former group would lead to larger or more widespread brain responses.

### 2.2. Differential Brain Responses During Tasks After Pre-Loaded with Sweet Beverages

Five studies investigated the differential effect of ingesting beverages with sugars and sweeteners on the brain responses to performing tasks subsequently [30][31][32][33][34]. Compared with subjects who were lean, subjects with obesity had larger brain responses when viewing food pictures after being pre-loaded with sugar than sweetener in the insula/operculum, cingulate, amygdala, hippocampus, and visual cortex [30]. Healthy subjects also had larger brain responses in the superior parietal gyrus when viewing general pictures after being pre-loaded with sugar compared to sweetener [31]. They also had larger responses in the hippocampus, precuneus, supramarginal gyrus, paracentral lobule, middle frontal gyrus, and

inferior parietal gyrus when recalling the memory of pictures after being pre-loaded with sugar compared to sweetener [31]. A larger response was observed in the insula/operculum, precentral gyrus, postcentral gyrus, and inferior temporal gyrus after being pre-loaded with sweetener rather than sugar [31]. Compared with pre-loading with sugar, tasting sweet solutions after pre-loading with sweetener would have larger brain responses in the insula/operculum, inferior frontal gyrus, and inferior parietal gyrus. Word encoding was also investigated. For patients with schizophrenia, word encoding would result in larger brain responses after being pre-loaded with sugar rather than sweetener, in the dorsolateral prefrontal cortex, parahippocampus, cuneus, and inferior temporal gyrus [33]. Finally, pre-loading with sugar would cause a larger response in the hippocampus than sweetener when healthy subjects performed an arithmetic task [28]. These examples showed that there was no simple phenomenon of whether ingesting sugar or sweetener would heighten the brain activity level when tasks were performed.

## 2.3. Differential Brain Activity Levels at Resting State After Pre-Loaded with Sweet Beverages

Four studies investigated the effects of ingesting beverages with sugars and sweeteners on the brain activity level at rest [35][36][37][38]. Kilpatrick et al. [35] found that there was a larger reductive effect of brain activity levels by ingesting sugars than sweeteners in the brainstem regions, such as the trigeminal nucleus, locus coeruleus, periaqueductal grey, and reticular nucleus. Sweeteners had a larger reductive effect in the nucleus tractus solitaries [35]. Though no significant differences in the functional connectivity were found between sugar and sweetener, across the conditions, subjects with obesity had a greater connectivity between the right lateral hypothalamus and a reward-related brain region, and weaker connectivity with homeostasis and gustatory-related brain regions than subjects who were lean. [35]. Van Opstal et al. [37] found that sugars reduced the activity level in the cingulate, ventral tegmental area, insula, lingual gyrus, fusiform gyrus, and striatum, whereas sweeteners had no effect. Besides, sucralose significantly increased the eigen vector centrality values in the cingulate, central gyri, and temporal lobe [37]. Another van Opstal et al. [38] study found that sugars reduced the activity level in the hypothalamus profoundly, whereas sweeteners reduced it much more mildly. In this study, they found that sugars increased the activity level shortly in the ventral tegmental area, whereas sweeteners increased it continuously [30]. Therefore, results from these two studies were a bit contradictory to each other in terms of the effect on the activity level in the ventral tegmental area. Meanwhile, Smeets et al. [36] also reported a prolonged reduced activity level in the hypothalamus caused by sugars but not by sweeteners. The brainstem, hypothalamus, and ventral tegmental area are targeted by various hormones and neural signals and are thus highly related to the processing of homeostatic energy balance, which is regulated in the long-term by leptin and insulin and in the short-term by circulating gastrointestinal hormones such as ghrelin, glucagon-like peptide 1 and peptide tyrosine [38]. There exists a complex energy-balance-regulating neural circuit that consists of the pituitary gland, brainstem, periaqueductal grey, thalamus, and various nuclei of the hypothalamus, and a key component of it is the melanocortin system in the arcuate nucleus of the hypothalamus [39]. Appetite is strongly modulated via the interplay between neuropeptide Y and proopiomelanocortin [39]. Therefore, it was reasonable to see that most studies reported an ingestion of energy-carrying sugary solutions led to a significant change in the activity level of these relevant regions.

## 2.4. Limitations of this Study and Future Perspectives

Many of the reviewed studies had small sample sizes, or reported uncorrected or false-discovery rate (FDR)-corrected statistics, which might be too liberal and lead to an increased false positive rate [40]. Some studies did not report the simple differential brain activation between sugar and non-nutritive sweetener (sugar > sweetener and vice versa), which would be crucial for conducting a meta-analysis. Moreover, non-fMRI studies, such as an EEG study by Crézé et al. [41], were omitted from this work. Readers should also be aware that the studies adopted different fasting durations, which further complicated any potential between-study comparisons, as longer fasts were associated with higher activity in the cerebellum, thalamus, and striatum in response to sweet taste [42]. Future studies, therefore, should recruit a larger sample size, adopt a standardized fasting duration (preferably 12 h overnight, which is the most common practice and brain responses are larger in the state of hunger), and reported results with familywise-error rate (FWE)-corrected statistics. Every study should report the differential brain activation between sugar and non-nutritive sweetener conditions regardless of the complexity of their experiment design. These measures would enable a meta-analysis pooling data across studies in a meaningful manner. In addition, future studies are recommended to recruit both males and females, as a recent review by Yunker et al. [43] also pointed out that many neuroimaging studies of NNS recruited same-sex cohorts only. That review also concluded that the differential brain responses elicited by NNS and caloric sweeteners did not seem to relate to metabolic findings [43]. As mentioned in the Introduction, humans could sense calorie differences in foods with equal sweetness [10] and that there are many relevant underlying signaling pathways such as those of SIRT1, Ulk1, and mTOR [11]. Therefore, future fMRI studies should also collect the metabolic data of subjects, such as changes in insulin levels.

## 3. Conclusions

This systematic review highlighted that there were few fMRI studies evaluating the differential cerebral processing of sugars and non-nutritive sweeteners, and their study designs were largely varied. The existence of inter-individual differences in response to sugar and non-nutritive sweeteners might also lead to the inconsistency and such as factors influencing individual differences should further be investigated. There was no consistent pattern suggesting that sugar or sweetener elicited larger brain responses. However, the brain regions often reported among these studies were the insula/operculum, cingulate, striatum, brainstem, hypothalamus, and ventral tegmental areas. They were related to taste processing, hedonic evaluations of food, and the processing of homeostatic energy balance. It should be noted that eight studies (40%) recruited fewer than 16 participants, a rudimentary threshold of recommended sample size for detecting the moderate effect size of fMRI findings [44], and hence their results might not be readily reproduced by future studies. With the large number of sugars and chemically distinctive sweeteners being consumed in our daily meals, more studies should be conducted as soon as possible to investigate their neural correlates, so that clinicians can further devise strategies to manage patients who require reduced sugar intake.

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