

Neuroimaging insights into the effects of non-nutritive sweeteners on appetite regulation: A systematic review

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ARTICLE INFO

Keywords:

Non-nutritive sweetener
Appetite regulation
Gut-brain axis
Glucose metabolism

ABSTRACT

Non-nutritive sweeteners (NNS) are increasingly used as low- or zero-calorie alternatives to sugar while maintaining sweetness. However, uncoupling sweet taste from caloric content may alter appetite regulation and promote food-seeking behavior, although the underlying neural mechanisms remain poorly understood. To address this, we conducted a systematic review in accordance with PRISMA guidelines. PubMed/MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials were searched up to June 2025 using terms related to NNS, neuroimaging and appetite regulation. Of 137 screened records, 21 neuroimaging reports met predefined PICO-based eligibility criteria. Eligible reports included healthy adults across weight categories and examined artificial or naturally occurring NNS (e.g., sucralose, erythritol) compared with nutritive sweeteners (NS; e.g., sucrose) or non-sweet controls (e.g., water). Outcomes included appetite-related brain responses measured using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), as well as associations with gut hormones, glucose metabolism, and eating behavior. NNS and NS both engaged gustatory and reward-related brain regions, with some reports showing reduced activity and lower pleasantness ratings for NNS. Hypothalamic activity and functional connectivity were also modulated by NNS intake, with no observed associations between brain responses and gut hormones or glucose metabolism in the available reports. Overall, the evidence remains limited and varies by NNS type, dose, delivery method, habitual intake, sex, weight status, and metabolic state. Future studies should investigate acute and long-term NNS consumption under real-world conditions with greater ethnic and demographic diversity, accounting for individual variability to better inform dietary guidelines.

1. Introduction

Excessive consumption of added sugar has become a major public health concern worldwide, as it is associated with a range of non-communicable diseases (NCDs), including type 2 diabetes (T2D), obesity, atherosclerotic cardiovascular disease (ASCVD), and cancer (Prinz, 2019). Thus, the World Health Organization (WHO) advises reducing sugar intake to less than 10% of total daily energy intake

(World Health Organization, 2015). As a dietary strategy, non-nutritive sweeteners (NNS) have gained global popularity (Russell et al., 2023). These low- or zero-calorie sugar alternatives offer a sweet taste without significantly affecting blood glucose levels (Moriconi et al., 2020). NNS can be classified as naturally occurring, including sugar alcohols (e.g., erythritol, xylitol) and plant-derived compounds (e.g., stevia), or as artificial, produced exclusively through chemical synthesis (e.g., sucralose, acesulfame K, aspartame) (Moriconi et al., 2020). In recent

This article is part of a special issue entitled: SSIB 2025 published in Appetite.

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<https://doi.org/10.1016/j.appet.2026.108803>

Received 11 February 2026; Received in revised form 7 August 2026; Accepted 13 October 2026

Available online 14 October 2026

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years, the use of NNS in beverages has increased more rapidly than added sugars, particularly in countries with policy interventions (Russell et al., 2023). Despite their widespread use, the WHO does not recommend NNS for weight management or the prevention of NCDs. Concerns persist regarding potential adverse effects, including ASCVD, impaired glycemic control, and an increased risk of cancer (World Health Organization, 2023). In addition, by decoupling sweetness from calories, NNS consumption may disrupt appetite regulation and promote food intake through homeostatic dysregulation (Egan, 2024), a concept known as the sweet uncoupling theory (Dalenberg et al., 2020).

Both sugars (nutritive sweeteners, NS) and NNS can activate sweet taste receptors in the oral cavity (Fig. 1), producing a similar sensory experience (Sukumaran & Palayyan, 2022). Sweet taste signaling extends beyond the tongue to the intestine, pancreas, and brain (Shi et al., 2025; Sukumaran & Palayyan, 2022) and is primarily mediated by G-protein-coupled receptors, such as the TAS1R2-TAS1R3 heterodimer (Shi et al., 2025). Other sweet taste pathways, such as the sodium-glucose cotransporter (SGLT1) and ATP-sensitive potassium (K_{ATP}) channels, respond only to NS, suggesting distinct metabolic effects (Sukumaran & Palayyan, 2022). NS stimulate enteroendocrine cells (EECs) in the gut to release postprandial hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), cholecystokinin (CCK), and

insulin, promoting satiety and regulating glucose metabolism (Wachsmuth et al., 2022). This metabolic response does not occur with artificial NNS like sucralose (Ahmad et al., 2020), while naturally occurring NNS such as sugar alcohols may trigger hormone release (Teyssie et al., 2022). Satiety signals from the gut are transmitted via vagal afferent neurons to the nucleus tractus solitarius (NTS) in the brainstem, then reach the arcuate nucleus (ARC) of the hypothalamus, a key region for regulating appetite and energy homeostasis (Wachsmuth et al., 2022). Acute consumption of NNS has been suggested to be involved in homeostatic regulation via the gut-brain axis, potentially through differences in post-ingestive satiety responses compared with NS (Moriconi et al., 2020). However, evidence on the effects of NNS intake on appetite regulation remains limited.

To address this gap, this systematic review synthesizes evidence from neuroimaging reports in healthy individuals across different weight categories, focusing on the neural mechanisms underlying appetite regulation and their interactions with metabolism and eating behavior. In this review, appetite refers to both homeostatic processes that regulate hunger and satiety via gut-brain signaling and non-homeostatic processes, such as hedonic and motivational mechanisms that drive food intake based on reward rather than physiological need (Ahn et al., 2022). The review also considers intra- and inter-individual factors that

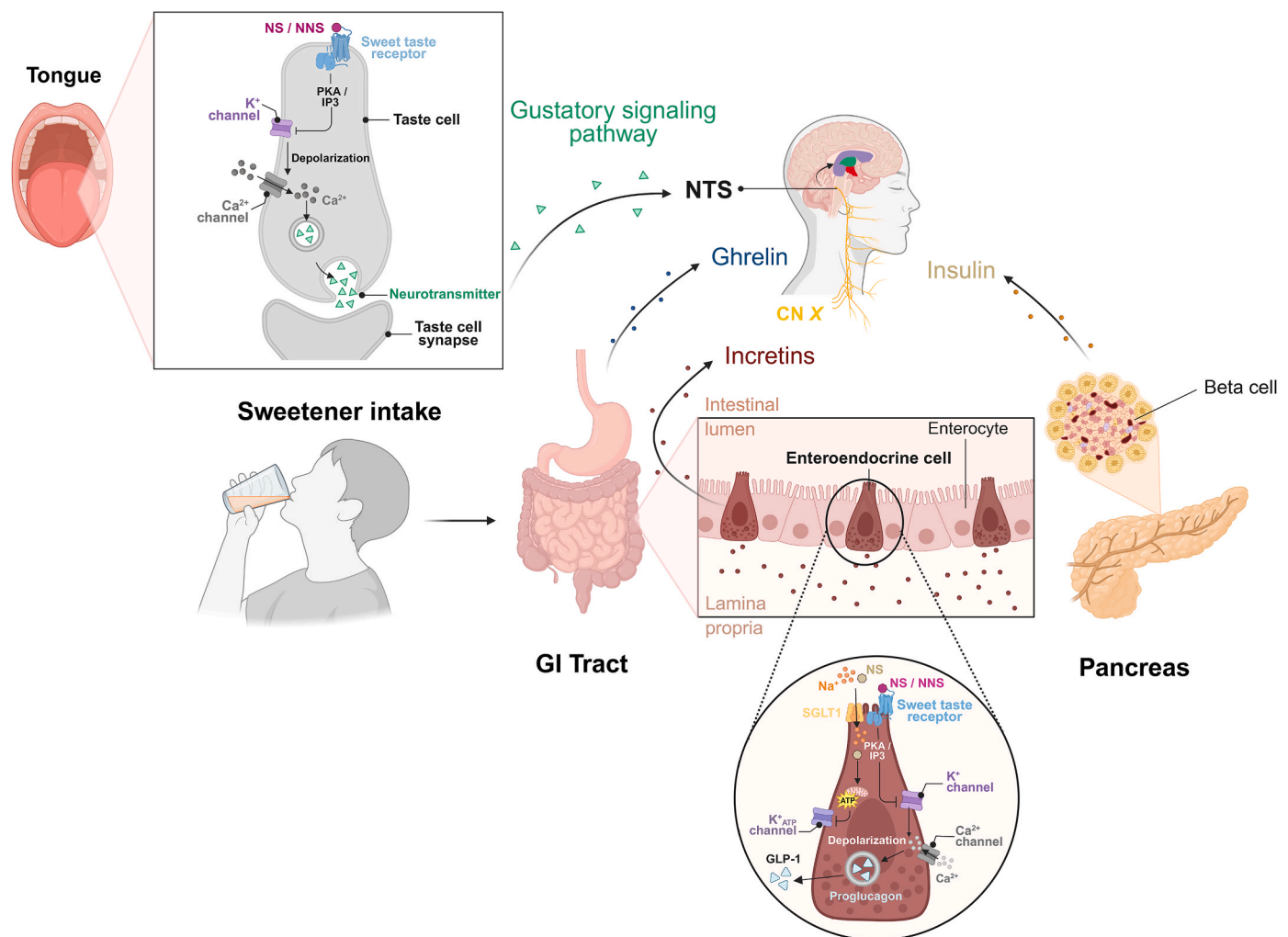


Fig. 1. Sweet taste signaling pathways in appetite control. Nutritive (NS) and non-nutritive sweeteners (NNS) activate intracellular pathways in taste cells, leading to depolarization and calcium (Ca^{2+}) release (von Molitor et al., 2021). Signals are transmitted via gustatory afferents to brain regions involved in taste perception (green) and reward processing (violet) (Long et al., 2025). NS additionally stimulate enteroendocrine cells (EECs) to release incretin hormones, which mediate satiety signaling to the nucleus tractus solitarius (NTS) via the vagus nerve and further to the hypothalamus (red) (Wachsmuth et al., 2022). Figure created with BioRender.com. Abbreviations: CN X, cranial nerve X (vagus nerve); GI, gastrointestinal; GLP-1, glucagon-like peptide-1; IP₃, inositol trisphosphate; PKA, protein kinase A; SGLT1, sodium-glucose cotransporter.

may influence appetite and eating, including sex, age, weight status, ethnicity, and metabolic state (Abdella et al., 2019; Bennett et al., 2022; Chen & Zeffiro, 2020; Holliday et al., 2025), as well as habitual NNS intake, which has been shown to shape appetite-related brain responses (Green & Murphy, 2012; Rudenga & Small, 2012). By highlighting key gaps and the role of individual variability, this review aims to guide future research on the effects of NNS on appetite regulation.

2. Methods

The current systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The protocol was prospectively registered with PROSPERO in July 2025 (registration number CRD420251042166, available at <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251042166>).

2.1. Eligibility criteria

To ensure alignment with the research objectives, inclusion criteria were defined according to the PICOS framework (population, intervention/exposure, comparison, outcomes, study design; Table 1) (Hosseini et al., 2024). Neuroimaging modalities were restricted to functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These techniques provide sufficient spatial resolution and enable assessment of both cortical and subcortical brain regions involved in appetite regulation, including taste, reward, and satiety processing (Farr et al., 2016). Only peer-reviewed articles published in English were considered.

Exclusion criteria included grey literature (e.g., dissertations, conference abstracts, preprints, and ongoing studies) and non-original research (systematic or narrative reviews, meta-analyses, case reports, and qualitative studies). Articles involving participants with acute or chronic conditions likely to affect brain function or metabolic regulation (e.g., T2D, autoimmune, cardiovascular, neurological, or gastrointestinal diseases, or cancer) were excluded. Neuroimaging studies using techniques such as electroencephalography (EEG), magnetoencephalography (MEG), functional near-infrared spectroscopy (fNIRS), or magnetic resonance spectroscopy (MRS) were excluded. Studies were also excluded if they did not involve interventions or exposures with NNS or if they assessed only metabolic or behavioral outcomes without reporting neuroimaging data.

Table 1
PICOS framework of review objectives: Population (P), Intervention/Exposure (I), Comparison (C), Outcomes (O), and Study design (S).

PICOS element	Description
Population (P)	Healthy humans (e.g., no type 2 diabetes, cardiovascular, gastrointestinal, neurological diseases etc.) with normal weight, overweight, or obesity, defined by BMI
Intervention/Exposure (I)	Artificial and/or naturally occurring non-nutritive sweetener (non-/low-caloric sweetener)
Comparison (C)	Nutritive sweetener (sugar), non-nutritive, non-sweet control (water), nutritive, non-sweet control (maltodextrin), non-nutritive sweetener + nutritive, non-sweet control
Outcomes (O)	<i>Neuroimaging</i> : brain activity, CBF, functional connectivity (fMRI), brain metabolism, and neurotransmitter systems (PET); <i>Metabolic</i> (if reported): blood insulin, glucose, gut hormonal levels (e.g., CCK, GLP-1, PYY); <i>Behavioral</i> (if reported): homeostatic (e.g., hunger), hedonic (e.g., liking) and motivational (e.g., wanting) responses
Study design (S)	Randomized experimental neuroimaging studies, including within- and between-subject designs

Notes. BMI, body mass index; CBF, cerebral blood flow; CCK, cholecystokinin; fMRI, functional magnetic resonance imaging; GLP-1, glucagon-like peptide-1; PET, positron emission tomography; PYY, peptide YY.

2.2. Search strategy

A systematic literature search was performed in PubMed/MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to June 2025, without restrictions on publication year. The search strategy combined free-text keywords with truncation across three primary topics: (1) non-nutritive sweeteners (e.g., sucralose, stevia, erythritol, xylitol), (2) neuroimaging methods or outcomes (e.g., fMRI, PET, cerebral blood flow [CBF], blood-oxygen-level-dependent [BOLD]), and (3) appetite regulation (e.g., gut hormone, insulin, glucose, food intake). The full search string for this systematic review is listed in [Supplementary Table S1](#). In addition, the reference lists of reports included, as well as relevant systematic reviews and meta-analyses on related topics, were manually screened to identify further eligible reports.

2.3. Study selection process

Throughout the manuscript, we distinguished between studies and reports: studies were defined as unique participant cohorts, whereas reports referred to individual publications, which could originate from the same study or include overlapping participant cohorts (Page et al., 2021). All records from the database searches were imported into Rayyan, a web-based platform used to assist with systematic review screening (Ouzzani et al., 2016). Retrieved records were first screened for duplicates. Two reviewers (A.B. and S.C.) independently screened the titles and abstracts against the predefined inclusion and exclusion criteria in a blinded manner to minimize potential selection bias. Any discrepancies were resolved through discussion with a third reviewer (Y. P.). Full texts of potentially eligible reports were checked for accessibility and for meeting eligibility criteria.

2.4. Data extraction

To ensure reliable data collection, three independent reviewers pilot-tested the extraction table on a representative 20% of reports (N = 4), resolving inconsistencies and refining the form prior to full extraction. Data were extracted by one reviewer (A.B.) using the pilot-tested extraction form, while two additional reviewers (S.C. and Y.P.) independently monitored the process and resolved any discrepancies through discussion. We extracted two tables with key characteristics and the summary of findings of the included reports. Detailed tables summarizing the statistical and methodological aspects of the neuroimaging reports are provided in [Supplementary Table S2](#).

2.5. Quality assessment

The quality of the included reports was assessed using an adapted version of the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, including 9 of the original 14 items relevant to the study types and focus of this systematic review. The following questions were used as criteria: (1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (4) Was a sample size justification, power description, or variance and effect estimates provided? (5) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure [NNS versus NS, water, or maltodextrin], and/or individual sweetness matching)? (6) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (7) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (8) Were the participants and outcome assessors blinded to the exposure status? (9) Were key potential

confounding variables (e.g., body mass index [BMI], age, or sex) measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

In addition, three criteria based on the recommendations of the Organization for Human Brain Mapping (OHBM) Committee on Best Practices in Data Analysis and Sharing (COBIDAS) were selected (Nichols et al., 2017): (10) Were acquisition parameters sufficiently reported (e.g., basic scanner information and sequence details)? (11) Were preprocessing steps adequately reported (e.g., head-motion correction)? (12) Were statistical analyses adequately reported, including statistical thresholds and correction for multiple comparisons?

Two independent reviewers (A.B. and S.C.) assessed the quality of each neuroimaging report using the 12 criteria, with disagreements resolved through discussion with a third reviewer (Y.P.). Each item was rated as not reported or not met (0), partially met (1), or fully met (2) (Nichol et al., 2018). The total score thus ranged from 0 to 24, with higher scores indicating higher methodological quality.

3. Results

3.1. Search results and study selection

The study selection process is summarized in Fig. 2. A total of 215

potentially relevant records were identified from searches in PubMed/MEDLINE (N = 71), Web of Science (N = 88), and CENTRAL (N = 55), and one potentially eligible record was identified through citation searching. After removing 78 duplicates, 137 records were screened by title and abstract. Based on predefined inclusion and exclusion criteria, 108 records were excluded, and three additional reports were excluded because they were abstract-only entries with no corresponding full-text publication (e.g., entries in CENTRAL). Of the 26 potentially eligible reports, five were excluded during full-text screening because they did not meet the PICOS eligibility criteria (i.e., intervention, comparator, or study design were out of scope). Overall, 21 reports met the eligibility criteria, representing 19 studies. Two reports (Chakravarti et al., 2025; Yunker et al., 2021) were derived from the same participant cohort but addressed different research questions and outcomes. Consequently, the final sample sizes differed because each publication applied analysis-specific inclusion criteria following participant dropout. Furthermore, van Rijn et al. (2016) combined participants from two previously published studies (Griffioen-Roose et al., 2013; van Rijn et al., 2015) and reported additional analyses using previously acquired BOLD data from the subset of participants available for the respective analyses (e.g., 18 of the 40 participants included in Griffioen-Roose et al. (2013)). To avoid double-counting, study characteristics were summarized based on the 19 studies, whereas

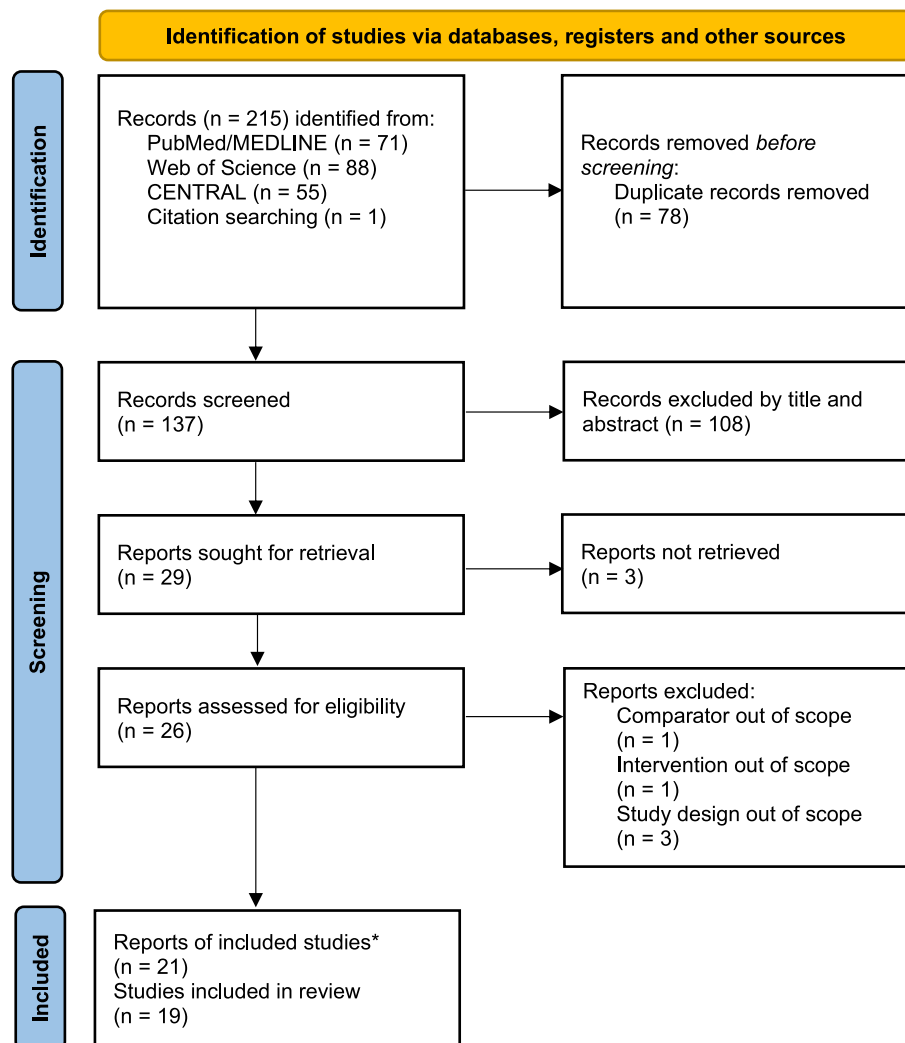


Fig. 2. PRISMA 2020 flow diagram illustrating the identification, screening, and inclusion of studies (Page et al., 2021). *The 21 included reports represent 19 studies. Two reports (Chakravarti et al., 2025; Yunker et al., 2021) originated from the same participant sample, and one report (van Rijn et al., 2016) combined participants from two previously reported studies (Griffioen-Roose et al., 2013; van Rijn et al., 2015).

outcome-specific findings were synthesized across the 21 reports because publications addressed distinct research questions or outcomes relevant to the aim of the systematic review.

3.2. Study characteristics

Across the 19 studies, a total of $N = 450$ adults were included in this systematic review (mean study sample size: $M = 24$, $SD = 13$). Overall, the cohort was balanced by sex, with 49.6% female and 50.4% male. For continuous variables, such as age and BMI, weighted means and pooled standard deviations were calculated based on study sample sizes. Participants were, on average, young adults with normal weight (weighted mean age: $M = 24$ years, $SD = 5$; weighted mean BMI: $M = 24.29$ kg/m², $SD = 4.34$). Only one study focused exclusively on individuals with obesity (BMI ≥ 30 kg/m²) (Farr, 2021), while the remaining studies included participants with normal weight (BMI 18.5–25.0 kg/m²). Six of the 19 studies included multiple weight groups, corresponding to seven of the 21 reports (Chakravartti et al., 2025; Connolly et al., 2013; Green

& Murphy, 2012; Meyer-Gerspach et al., 2022; Tryon et al., 2015; Wang et al., 2014; Yunker et al., 2021). These reports allowed examination of the effects of BMI or weight status on outcomes following NNS consumption.

Across the 19 studies, sucralose was the most studied artificial NNS ($N = 9$), followed by aspartame ($N = 3$) and saccharin ($N = 2$). Other combinations included sucralose + acesulfame K ($N = 1$) and aspartame + acesulfame K + cyclamate + saccharin ($N = 1$). Naturally occurring NNS were less frequently investigated, including erythritol ($N = 3$), stevia ($N = 2$), and xylitol ($N = 1$). The most common comparators were nutritive sweeteners (sucrose [$N = 12$], glucose [$N = 6$], fructose [$N = 2$]), followed by water ($N = 8$), maltodextrin ($N = 3$), and sucralose + maltodextrin ($N = 2$) (Table 2). All studies investigated the effects of NNS delivered in beverages. Eighteen of the 19 studies administered NNS orally, either during neuroimaging (via sipping) or shortly before scanning (post-ingestion). Only one study used intragastric administration (Meyer-Gerspach et al., 2022). In the eight studies assessing post-ingestion brain responses, NNS were dissolved in ~300 mL of

Table 2
Characteristics of the included reports and participants.

Author, year	Study design	Neuro-imaging modality	Participants N (% female, age in years mean $\pm$ SD, weight status [%])	NNS intervention	Comparator	Delivery	Metabolic state
Budzinska et al. (2024)	WSD	fMRI	30 (0%, 24 $\pm$ 4 ^a , NW)	Erythritol, Sucralose	Sucrose, Water	Oral	Fasted
Budzinska et al. (2025)	WSD	fMRI	30 (0%, 23 $\pm$ 1, NW)	Erythritol	Sucrose, Water	Oral	Fasted
Chakravartti et al. (2025) [†]	WSD	fMRI	75 (57%, 23 $\pm$ 4, NW [37%]/OW [32%]/OB [31%])	Sucralose	Sucrose, Water	Oral	Fasted
Connolly et al. (2013)	WSD	fMRI	20 (100%, 26 $\pm$ 5 ^a , NW [50%]/OB [50%])	Truvia (stevia-based)	Sucrose	Oral	Fasted
Dalenberg et al. (2020)	BSD	fMRI	39 (54%, 28 $\pm$ 4, NW)	Sucralose	Sucrose, Sucralose + Maltodextrin	Oral	Mixed ^b
Farr (2021)	WSD	fMRI	5 (40%, 52 $\pm$ 6, OB)	Aspartame	Regular Cola ^c , Water	Oral	Fasted
Frank et al. (2007)	WSD	fMRI	12 (100%, 27 $\pm$ 6, NW)	Sucralose	Sucrose	Oral	Satiated
Green & Murphy (2012)	WSD	fMRI	24 (58%, 23 $\pm$ 3, NW/OW/OB [NR])	Saccharin	Sucrose	Oral	Fasted
Griffioen-Roose et al. (2013)*	WSD	fMRI	40 (63%, 21 $\pm$ 2, NW)	Sucralose, Sucralose + Acesulfame-K	Sucrose	Oral	Fasted
Haase et al. (2009)	WSD	fMRI	18 (50%, 21 $\pm$ 1, NW)	Saccharin	Sucrose	Oral	Mixed ^b
Meyer-Gerspach et al. (2022)	WSD	fMRI	20 (50%, 28 $\pm$ NR, NW/OW/OB [NR])	Erythritol, Xylitol	Glucose, Water	Intra-gastric	Fasted
Smeets et al. (2005a)	WSD	fMRI	5 (0%, 20 $\pm$ 6 ^a , NW)	Aspartame	Glucose, Maltodextrin, Water	Oral	Fasted
Smeets et al. (2011)	WSD	fMRI	10 (0%, 23 $\pm$ 3, NW)	Aspartame + Acesulfame K + Cyclamate + Saccharin	Sucrose	Oral	Fasted
Stamataki et al. (2022)	WSD	fMRI	18 (NR, 26 $\pm$ 5, NW)	Stevia	Glucose, Maltodextrin, Water	Oral	Fasted
Tryon et al. (2015)	BSD	fMRI	19 (100%, 27 $\pm$ 7, NW/OW/OB [NR])	Aspartame	Sucrose	Oral	NR
van Opstal et al. (2019a)	WSD	fMRI	16 (0%, 22 $\pm$ 1, NW)	Sucralose	Glucose, Fructose, Sucrose, Water	Oral	Fasted
van Opstal et al. (2021)	WSD	fMRI	20 (0%, 22 $\pm$ 1, NW)	Sucralose	Allulose, Glucose, Fructose	Oral	Fasted
van Rijn et al. (2015)*	WSD	fMRI	30 (100%, 22 $\pm$ 3, NW)	Sucralose	Maltodextrin, Sucralose + Maltodextrin	Oral	Mixed ^b
van Rijn et al. (2016) (study 1)*	WSD	fMRI	30 (100%, 22 $\pm$ 3, NW)	Sucralose	Sucralose + Maltodextrin	Oral	Mixed ^b
van Rijn et al. (2016) (study 2)*	WSD	fMRI	18 (17%, 22 $\pm$ 2, NW)	Sucralose, Sucralose + Acesulfame-K	Sucrose	Oral	Fasted
Wang et al. (2014)	WSD	PET	19 (NR, NR, NW/OW/OB [NR])	Sucralose	Glucose	Oral	Fasted
Yunker et al. (2021) [†]	WSD	fMRI	74 (58%, 23 $\pm$ 4, NW [37%]/OW [32%]/OB [31%])	Sucralose	Sucrose, Water	Oral	Fasted

Notes. BSD, between-subject design; fMRI, functional magnetic resonance imaging; NR, not reported; NNS, non-nutritive sweetener; NW, normal weight; OB, obesity; OW, overweight; PET, positron emission tomography; WSD, within-subject design.

[†] Reports from the same participant cohort with distinct neuroimaging outcomes.

* Reports based on overlapping participant samples and reporting additional analyses.

^a Standard deviation (SD) not reported, calculated from standard error of the mean (SEM) using $SD = SEM \times \sqrt{n}$.

^b Metabolic state varied across participants, including both fasted and satiated measurements.

^c Type of sweetener not reported.

Table 3

Neuroimaging findings of non-nutritive sweetener (NNS) consumption assessed using functional magnetic resonance imaging (fMRI). Comparisons include baseline, nutritive sweeteners (NS), water (non-nutritive, non-sweet control), and maltodextrin (nutritive, non-sweet control).

Author, year	Analysis type	Neuroimaging outcome (task)	NNS vs. baseline	NS vs. baseline	NNS vs. NS	Water vs. baseline	NNS vs. water	Maltodextrin vs. baseline	NNS vs. maltodextrin
Task-based fMRI									
Gustatory processing (intra-oral delivery)									
Dalenberg et al. (2020)	Whole-brain	BOLD activity (sweet, sour, salty, savory stimuli)	-	-	Overall ↔	-	-	-	-
Frank et al. (2007)	Whole-brain; ROI	BOLD activity (sweet stimuli)	FO/AI, SFG ↑	ACC, FO/AI, SN/VTA, striatum, SFG ↑	ACC, FO/AI, striatum, SFG ↓	-	-	-	-
Griffioen-Roose et al. (2013)*	Whole-brain; ROI	BOLD FC (sweet stimuli)	FO/AI activity changes positively correlated with pleasantness slope	FO/AI – ACC, striatum, thalamus ↑	FO/AI – striatum ↑	-	-	-	-
		BOLD activity (sweet stimuli after repeated exposure)	-	-	Middle cingulum, rolandic operculum ↓; precentral gyrus activity differences ↓ positively correlated with wanting ratings	-	-	-	-
Haase et al. (2009)	Whole-brain; ROI	BOLD activity (sweet stimuli)	Hippocampus, parahippo-campus, thalamus ↑ (during hunger vs. satiety)	Amygdala, hippocampus, insula, OFC, parahippo-campus, SN, thalamus ↑ (during hunger vs. satiety)	Insula, OFC ↓ (during hunger vs. satiety)	-	-	-	-
Smeets et al. (2011)	Whole-brain; ROI	BOLD activity (sweet stimuli after post-ingestion)	Amygdala, insula, OFC, striatum ↑	Amygdala, insula, OFC, striatum ↑	Amygdala, OFC ↑; insula ↔; striatum ↓	-	-	-	-
van Rijn et al. (2016) (study 1)*	Whole-brain; ROI	BOLD activity (sweet stimuli)	-	-	ACC, amygdala, right caudate activity differences ↓ (during hunger) negatively correlated & left caudate activity differences ↓ (during satiety) positively correlated with reward sensitivity	-	-	-	-
van Rijn et al. (2016) (study 2)*	Whole-brain; ROI	BOLD activity (sweet stimuli)	-	-	No correlation between ACC, amygdala, caudate activity differences ↔ and reward sensitivity	-	-	-	-
Hedonic evaluation (intra-oral delivery)									
Budzinska et al. (2024)	Whole-brain; ROI	BOLD activity (sweet taste liking)	-	-	Overall ↔	-	Amygdala ↑; Sucralose: FO, inferior parietal cortex, insula, MCC, midbrain ↑; ACC, dmPFC, OFC, SFG ↓; differences correlated with sweetness liking ratings	-	-
Budzinska et al. (2025)	Whole-brain; ROI	BOLD FC (sweet taste liking)	-	-	Overall ↔	-	Overall ↔	-	-
		BOLD activity (sweet taste liking after caloric labeling)	-	-	Overall ↔	-	DS, hypothalamus, lateral OFC, VS, VTA/SN ↑; medial OFC ↓	-	-

(continued on next page)

Table 3 (continued)

Author, year	Analysis type	Neuroimaging outcome (task)	NNS vs. baseline	NS vs. baseline	NNS vs. NS	Water vs. baseline	NNS vs. water	Maltodextrin vs. baseline	NNS vs. maltodextrin
Green & Murphy (2012)	Whole-brain; ROI	BOLD activity (sweet taste liking)	-	-	OFC (NNS non-consumers) ↑, (NNS regular consumers) ↔; caudate activity to NNS exposure negatively correlated with regular NNS consumption/week	-	-	-	-
van Rijn et al. (2015)*	Whole-brain; ROI	BOLD activity (sweet taste liking)	-	-	Overall ↔	-	-	-	Overall ↔
Stress modulation (2 weeks regular consumption)									
Tryon et al. (2015)	ROI	BOLD activity (stress induction task)	-	-	Hippocampus ↓	-	-	-	-
Food cue reactivity (post-ingestion)									
Connolly et al. (2013)	ROI	BOLD activity (visual food cue task)	Amygdala, hippocampus, insula, thalamus ↑	Amygdala, hippocampus, insula, thalamus ↑	Overall ↔	-	-	-	-
Farr (2021)	Whole-brain; ROI	BOLD activity (visual food cue task)	-	-	dIPFC ↓; insula ↑	-	Caudate ↑	-	-
Yunker et al. (2021)†	ROI	BOLD activity (visual food cue task)	-	-	Amygdala, DS, hippocampus, hypothalamus, insula, MFC, NAcc, OFC ↔	-	Amygdala, DS, hippocampus, hypothalamus, insula, MFC, NAcc, OFC ↔	-	-
rs-fMRI (post-ingestion)									
Smeets et al. (2005a)	ROI	BOLD activity	Hypothalamus ↔	Hypothalamus ↓	Hypothalamus ↑	Hypothalamus ↔	Hypothalamus ↔	Hypothalamus ↔	Hypothalamus ↔
van Opstal et al. (2019a)	ROI	BOLD activity	Hypothalamus ↓ (transient); VTA ↑ (transient) Hypothalamus activity changes negatively correlated with perceived sweetness ratings	Hypothalamus ↓; VTA ↑ (transient)	-	Hypothalamus, VTA ↑	Hypothalamus, VTA ↓	-	-
van Opstal et al. (2021)	Whole-brain	BOLD activity	Basal ganglia, cingulate cortex, insula ↔	Basal ganglia, cingulate cortex, insula ↓	-	-	-	-	-
		BOLD FC	Salience network ↔	Glucose: salience network ↑; changes positively correlated with wanting ratings	-	-	-	-	-
Multimodal fMRI (post-ingestion)									
Chakra-vartti et al. (2025)†	ROI	rs-CBF	No correlation of hypothalamus activity changes with blood glucose or hunger	Hypothalamus activity changes negatively correlated with changes in blood glucose level & hunger	Hypothalamus ↑	-	Hypothalamus ↑	-	-
		Task-based BOLD FC (visual food cue task)	-	-	Hypothalamus – ACC ↑	-	Hypothalamus – superior parietal lobule ↑	-	-
Meyer-Gerspach et al. (2022)	Whole-brain; ROI	rs-CBF	Xylitol: Hypo-thalamus ↑	Hypothalamus ↓	Xylitol: Hypothalamus ↑	Hypothalamus ↔	-	-	-
		rs-BOLD FC	Erythritol: OFC (overall) ↓; Xylitol: Putamen (overall) ↑	OFC (overall) ↑; Putamen (overall) ↓	Erythritol: OFC (overall) ↓; Xylitol: Putamen (overall) ↑	Insula, OFC (overall) ↓; NAcc, Putamen (overall) ↑	Erythritol: Insula (overall) ↓; Xylitol: Putamen	-	-

(continued on next page)

Table 3 (continued)

Author, year	Analysis type	Neuroimaging outcome (task)	NNS vs. baseline	NS vs. baseline	NNS vs. NS	Water vs. baseline	NNS vs. water	Maltodextrin vs. baseline	NNS vs. maltodextrin
Stamataki et al. (2022)	Whole-brain	rs-BOLD activity	Insula, middle cingulate, pre/postcentral gyrus, SMA, temporal gyrus ↓ (sustained) Overall ↔	Insula, middle cingulate, pre/postcentral gyrus, SMA, temporal gyrus ↓ (transient) Overall ↔	Insula, middle cingulate, pre/postcentral gyrus, SMA, temporal gyrus ↓ Overall ↔	Insula, middle cingulate, pre/postcentral gyrus, SMA, temporal gyrus ↓ (transient) Overall ↔	(overall) ↓; NAcc, OFC (overall) ↑ Insula, middle cingulate, pre/postcentral gyrus, SMA, temporal gyrus ↓ Overall ↔	ACC, caudate, insula, putamen, SFG ↓ (transient) Overall ↔	ACC, caudate, insula, putamen, SFG ↓ Overall ↔
		Task-based BOLD activity (visual food cue task)	Overall ↔	Overall ↔	Overall ↔	Overall ↔	Overall ↔	Overall ↔	Overall ↔

Notes. Arrows indicate direction of effect for each brain response: ↓ = decrease/lower, ↑ = increase/higher, ↔ = no change/difference. ACC, anterior cingulate cortex; AI, anterior insula; BOLD, blood oxygen level dependent; dIPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; DS, dorsal striatum; FC, functional connectivity; fMRI, functional magnetic resonance imaging; FO, frontal operculum; MCC, middle cingulate cortex; MFC, medial frontal cortex; NAcc, nucleus accumbens; NNS, non-nutritive sweetener; NS, nutritive sweetener; OFC, orbitofrontal cortex; ROI, region of interest; rs, resting-state; SFG, superior frontal gyrus; SMA, supplementary motor area; SN, substantia nigra; VS, ventral striatum; VTA, ventral tegmental area. † Reports from the same participant cohort with distinct neuroimaging outcomes. *Reports based on overlapping participant samples and reporting additional analyses.

water, except in one study that used 165 mL of a sugar-free milkshake (van Opstal et al., 2021). NNS doses were individually matched or calculated based on their relative sweetening power to achieve sweetness equivalent to the NS comparator. The included studies used different approaches to select NS amounts, with three following the oral glucose tolerance test (OGTT) using 75 g (Meyer-Gerspach et al., 2022; Smeets et al., 2005a; Yunker et al., 2021), and five using high-NS soft drinks (Connolly et al., 2013; Farr, 2021) or comparable amounts ranging from 20 to 50 g (Stamataki et al., 2022; van Opstal et al., 2019a, 2021).

3.3. Quality of the included reports

The neuroimaging reports included in this review had quality sum scores ranging from 16 to 24 (mean 19.6) on a 0-24 scale, indicating overall moderate-to-high methodological quality (Supplementary Table S3). All reports clearly stated their research question or objective and eligibility criteria for participant selection. However, only eight of 21 reports described a sample size justification (Meyer-Gerspach et al., 2022) or power calculation (Budzinska et al., 2024, 2025; Chakravarti et al., 2025; Dalenberg et al., 2020; Stamataki et al., 2022; van Opstal et al., 2021; Yunker et al., 2021). All reports compared NNS exposure with at least one comparator (e.g., NS, water, or maltodextrin), but only five applied individual sweetness matching via varying NNS concentrations (Budzinska et al., 2024, 2025; Chakravarti et al., 2025; Frank et al., 2007; Yunker et al., 2021). Exposure and outcome measures were adequately reported in 20 of 21 reports. However, one report did not specify the type or amount of NNS and NS used (Farr, 2021). Nine reports used a double-blind design (Chakravarti et al., 2025; Connolly et al., 2013; Dalenberg et al., 2020; Meyer-Gerspach et al., 2022; Stamataki et al., 2022; Tryon et al., 2015; van Opstal et al., 2019a, 2021; Yunker et al., 2021), whereas the remaining 12 either blinded participants only or did not clearly describe blinding procedures. Fifteen of 21 reports described BMI, age, and sex, and five of these adjusted for these confounders in their analyses (Chakravarti et al., 2025; Connolly et al., 2013; Haase et al., 2009; Wang et al., 2014; Yunker et al., 2021).

Acquisition parameters were sufficiently reported in all included neuroimaging reports, except for one that did not provide information on the scanner model or field strength (Smeets et al., 2011). Neuroimaging preprocessing procedures were clearly described in nearly all reports, although motion correction was not explicitly reported in one report (Wang et al., 2014). Statistical analyses of neuroimaging measures were reported in 15 of the 21 reports. Five reports did not report correction for multiple comparisons (Frank et al., 2007; Griffioen-Roose et al., 2013; van Opstal et al., 2019a; van Rijn et al., 2015, 2016), and one report described correction for selected region-of-interest (ROI) analyses (Smeets et al., 2011).

3.4. Brain responses to non-nutritive sweeteners

Of the 21 included reports, 20 employed fMRI to assess the effects of NNS in beverages on brain activity and functional connectivity (FC), while one used PET with the [¹¹C]raclopride radiotracer to examine dopamine signaling. Task-based BOLD activity was assessed in 16 of the 20 fMRI reports, whereas six used resting-state fMRI to examine BOLD activity (n = 4) or CBF (n = 2). Three of the fMRI reports used multi-modal MRI approaches: two combined CBF measurements with BOLD imaging (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022), whereas one combined resting-state and task-based BOLD imaging (Stamataki et al., 2022). The effects of NNS were compared with baseline brain responses or with other comparators such as NS, water, or maltodextrin (Table 3).

3.4.1. Task-based functional magnetic resonance imaging (fMRI) reports
Among the 16 of 21 included reports that used task-based fMRI, six investigated gustatory processing, four examined hedonic evaluation,

and five assessed reactivity to visual food cues. One report additionally examined the effects of a stress modulation task on brain activity following two weeks of NNS versus NS consumption to investigate stress response involved in eating behavior (Tryon et al., 2015). Gustatory processing involved intra-oral delivery of sweet stimuli (sipping) during scanning; hedonic evaluation additionally included in-scanner ratings of the pleasantness (liking) of these stimuli. Food cue reactivity was assessed after drink ingestion by presenting participants with visual food cues (e.g., high- versus low-calorie items) and non-food control images.

3.4.1.1. Gustatory processing. Six of the 16 task-based fMRI reports assessed BOLD activity during the tasting of sweet stimuli delivered intra-orally. Three reports found increased activity in gustatory regions for both sweet stimuli, with lower responses for NNS than for NS (Frank et al., 2007; Griffioen-Roose et al., 2013; Haase et al., 2009). Frank et al. (2007) additionally reported that activity in the primary taste cortex was associated with higher pleasantness ratings, and that FC with the striatum was higher for NNS than for NS. Griffioen-Roose et al. (2013) further observed lower activity in brain regions involved in somatosensory processing and motor control for NNS than for NS. In four reports, sweet stimuli engaged reward-related brain regions during tasting, with lower activity observed for NNS compared to NS (Frank et al., 2007; Haase et al., 2009; Smeets et al., 2011; van Rijn et al., 2016). Two of these reports identified modulation by metabolic state (Haase et al., 2009; van Rijn et al., 2016). In addition, van Rijn et al. (2016) reported associations with reward sensitivity, as measured by the Behavioral Inhibition System/Behavioral Activation System (BIS/-BAS) questionnaire. One report found no significant effects of short-term NNS consumption on sweet taste-related brain activity (Dalenberg et al., 2020). None of the reports included comparisons with non-sweet control stimuli, such as water or maltodextrin.

3.4.1.2. Hedonic evaluation. Four of the 16 task-based fMRI reports examined brain responses associated with liking ratings during intraloral sweet taste delivery (Budzinska et al., 2024, 2025; Green & Murphy, 2012; van Rijn et al., 2015). None reported significant differences in BOLD activity or FC during hedonic evaluation between NNS and caloric stimuli, such as NS or maltodextrin. However, NNS elicited higher hypothalamic activity and greater responses in reward-related and gustatory regions than water, used as a non-sweet control (Budzinska et al., 2024, 2025). Accounting for individual differences, Green and Murphy (2012) reported that regular NNS consumers showed no overall effect, whereas non-consumers exhibited greater orbitofrontal cortex (OFC) activity in response to NNS compared with NS. This report additionally identified an association between higher weekly NNS intake and lower caudate responses (Green & Murphy, 2012).

3.4.1.3. Visual food cue reactivity. Five of the 16 task-based fMRI reports investigated brain responses to visual food cues following ingestion of NNS-containing beverages, using varying doses. One of these analyzed hypothalamic FC, reporting stronger connectivity to reward-related and somatosensory regions compared with NS and water, respectively (Chakravarti et al., 2025). Another report observed increased BOLD activity in gustatory and reward-related regions following NNS compared with NS or water, respectively, and reduced dorsolateral prefrontal cortex (dlPFC) activity in response to visual food versus non-food cues after consumption of a diet versus a regular soft drink (Farr, 2021). The remaining reports found no overall changes in BOLD activity following acute NNS consumption (Connolly et al., 2013; Stamataki et al., 2022; Yunker et al., 2021). Sex- and weight-group effects were observed in one of these reports, with females and individuals with obesity showing stronger activity in reward-related regions in response to hedonic visual food cues following NNS compared with NS. In contrast, males and individuals with normal weight showed no significant differences (Yunker et al., 2021).

3.4.2. Resting-state functional magnetic resonance imaging (fMRI) reports

Six of the 20 fMRI reports assessed resting-state BOLD and CBF responses following acute NNS ingestion, with three reporting effects in gustatory and reward-related regions involved in decision-making and food-seeking behavior. One of these found lower BOLD activity in taste and somatosensory regions after NNS compared with NS, water, and maltodextrin (Stamataki et al., 2022). Another report observed increased midbrain activity for both sweet stimuli, with different time-dependent effects, showing sustained responses after NNS and transient responses after NS (van Opstal et al., 2019a). Two reports further analyzed FC, with one reporting region-specific FC changes following naturally occurring NNS compared with NS and water (Meyer-Gerspach et al., 2022). In contrast, the other report found no effects of NNS on either BOLD activity or FC, whereas ingestion of a glucose-containing drink increased FC within the salience network, which was associated with higher wanting ratings (van Opstal et al., 2021).

Four of six resting-state fMRI reports investigated hypothalamic responses to NNS ingestion. Findings were inconsistent, with reports showing either no change (Smeets et al., 2005a), transient decrease (van Opstal et al., 2019a), or an increase in hypothalamic activity relative to baseline (Meyer-Gerspach et al., 2022). In contrast, NS ingestion consistently reduced hypothalamic activity across reports, as reflected by decreases in BOLD activity (Smeets et al., 2005a; van Opstal et al., 2019a) and CBF (Meyer-Gerspach et al., 2022). Overall, NNS elicited greater hypothalamic responses than NS in three of four reports (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022; Smeets et al., 2005a). However, when compared with water, findings were inconsistent, with reports showing no differences (Smeets et al., 2005a), reductions (van Opstal et al., 2019a) or increases (Chakravarti et al., 2025). Furthermore, higher perceived sweetness of stimuli predicted lower hypothalamic activity (van Opstal et al., 2019a).

3.4.3. Positron emission tomography (PET) reports

Only one PET study has investigated the impact of acute NNS beverage intake on dopamine signaling compared to NS, using the [¹¹C] raclopride radiotracer, which competes with endogenous dopamine at D₂/D₃ receptors. Dopamine release in the nucleus accumbens (NAcc) was lower following NNS compared with NS, suggesting reduced reward signaling. Interestingly, beyond sweet taste, the caloric content of NS was associated with higher dopamine signaling in individuals with normal weight, whereas those with obesity exhibited lower dopamine responses, potentially promoting food-seeking behavior (Wang et al., 2014).

3.5. Metabolic responses to non-nutritive sweeteners

This systematic review aims to understand the bidirectional communication between appetite-related metabolic processes and brain responses in the context of NNS ingestion. However, only three of the 21 reports directly examined this relationship, while three others reported gut hormone, insulin, or glucose responses to NNS without assessing their interaction with brain responses (Supplementary Tables S4–S6).

3.5.1. Appetite-related hormones

Evidence for the effects of NNS on gut hormones in neuroimaging reports was limited, with only three of the 21 reports describing inconsistent findings that varied by sweetener type. One report observed lower GLP-1 and higher ghrelin concentrations after NNS compared with NS, with responses similar to water (Yunker et al., 2021). In contrast, another report found that intragastric administration of naturally occurring NNS (e.g., xylitol) increased PYY and CCK concentrations, reaching levels comparable to NS and higher than those following water ingestion (Meyer-Gerspach et al., 2022). There was no significant correlation between GLP-1 (Chakravarti et al., 2025) or CCK levels and hypothalamic blood flow (Meyer-Gerspach et al., 2022) for NNS or NS.

No significant associations were observed for PYY or ghrelin, nor for other brain regions.

3.5.2. Glucose metabolism

Four reports investigated the acute effects of NNS and one the short-term effects on glucose metabolism. Findings were consistent, showing lower blood glucose and insulin levels following acute NNS beverage intake compared with caloric stimuli such as NS (Meyer-Gerspach et al., 2022; Smeets et al., 2005a; van Opstal et al., 2019a; Yunker et al., 2021) or maltodextrin (Smeets et al., 2005a). Artificial sweeteners elicited responses similar to those observed following water, whereas one report showed increased blood glucose and insulin levels after intragastric administration of the naturally occurring NNS xylitol compared with water (Meyer-Gerspach et al., 2022). For short-term effects on insulin sensitivity, one report found increased insulin levels during an OGTT following two weeks of sucralose plus maltodextrin consumption, whereas no such effect was observed with NNS alone (Dalenberg et al., 2020). This effect was accompanied by reduced responses to both NNS and NS in reward-related regions. Other reports investigating body-brain interactions reported that rising blood glucose levels were associated with decreased hypothalamic blood flow following NS (Chakravarti et al., 2025), whereas changes after NNS showed no significant relationship (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022).

3.6. Behavioral responses to non-nutritive sweeteners

The interaction between behavioral and brain responses has been rarely studied in the context of appetite regulation following NNS intake. Eighteen of 21 reports focused on food-related homeostatic and hedonic behavioral responses, either after ingestion or during direct sipping of the sweet solutions (Supplementary Tables S7–S9). Cognitive outcomes, such as inhibitory control and memory, were evaluated in one report and showed no differences between NNS and NS (Farr, 2021).

3.6.1. Homeostatic responses: hunger, satiety and food intake

When sweet taste is uncoupled from caloric content, this may alter homeostatic responses. However, eight of 10 reports observed no differences in subjective ratings of hunger, satiety, fullness, or prospective food intake (Connolly et al., 2013; Farr, 2021; Griffioen-Roose et al., 2013; Meyer-Gerspach et al., 2022; Smeets et al., 2011; Stamataki et al., 2022; van Opstal et al., 2019a, 2021). In contrast, the two remaining reports, derived from the same study, found positive findings, showing greater food intake at an ad libitum buffet (Yunker et al., 2021) and higher subjective hunger after acute NNS versus NS intake (Chakravarti et al., 2025). No association with hypothalamic responses was found after NNS, whereas after NS, lower hunger ratings correlated with reduced hypothalamic blood flow in one report (Chakravarti et al., 2025). NNS and non-sweet controls (e.g., water or maltodextrin) did not differ in homeostatic behavioral responses (Chakravarti et al., 2025; Farr, 2021; Meyer-Gerspach et al., 2022; Stamataki et al., 2022; Yunker et al., 2021), except for one report showing lower subjective hunger after acute NNS intake compared with water (van Opstal et al., 2019a).

3.6.2. Hedonic and motivational responses: food-related liking, wanting and choices

Twelve of the 21 reports measured perceived sweetness and reported no significant differences between NNS and NS. Nevertheless, even when sweetness was perceived as equivalent, subjective liking or pleasantness was lower for NNS in five reports (Budzinska et al., 2024, 2025; Griffioen-Roose et al., 2013; Smeets et al., 2011; van Opstal et al., 2019a). Food-related wanting and choices did not differ between NNS and NS, although one report showed lower choices for NNS drinks after tasting (Griffioen-Roose et al., 2013). No significant differences in hedonic or motivational responses were observed between NNS and either water (Farr, 2021; van Opstal et al., 2019a) or maltodextrin (van Rijn

et al., 2015).

Brain responses to sweet stimuli were associated with perceptual, hedonic, and motivational measures. One report observed that higher perceived sweetness was associated with reduced hypothalamic activity, independent of calories (van Opstal et al., 2019a). Sweetness pleasantness showed a bidirectional relationship, predicting activity in the primary taste cortex in one report (Frank et al., 2007) and being mediated by reward, gustatory, and homeostatic regions in two other reports (Budzinska et al., 2024, 2025). Lower choice for NNS than NS was associated with lower activity in the precentral gyrus, a region involved in sensorimotor processing (Griffioen-Roose et al., 2013).

3.7. Individual factors influencing the effects of non-nutritive sweeteners

Reports showing overall null effects identified differences in specific subgroups, such as by sex, body weight (Connolly et al., 2013; Yunker et al., 2021) or habitual NNS intake (Green & Murphy, 2012), or were influenced by intra-individual factors, including metabolic state (van Rijn et al., 2015). No effects of age or ethnicity were investigated, likely reflecting the narrow age range of young adults and the limited ethnic diversity in the studies.

3.7.1. Sex

Two reports from the same study found stronger effects of NNS on homeostatic and hedonic responses in females, including greater activation of the medial frontal cortex (MFC) and OFC in response to high-calorie or sweet food cues compared with control cues (Yunker et al., 2021), as well as higher hypothalamic blood flow relative to males (Chakravarti et al., 2025). Yunker et al. (2021) additionally observed increased energy intake during an ad libitum buffet in females, whereas males showed no difference between NNS and NS. In contrast, no sex differences were found in appetite-related metabolic responses, including blood glucose, insulin, GLP-1, ghrelin, or PYY, following NNS versus NS ingestion (Yunker et al., 2021). Because menstrual cycle phase can influence appetite regulation, both reports controlled for this factor by including female participants in the follicular phase (Chakravarti et al., 2025; Yunker et al., 2021).

3.7.2. Weight status

In total, four reports investigated whether weight status modulates the effects of NNS. Higher BMI has been associated with differences in brain and behavioral responses to NNS, particularly in relation to reward processing and homeostatic regulation. Two of these reports observed that, following NNS versus NS consumption, individuals with obesity showed greater brain responses to visual food compared with non-food cues in regions involved in reward-related decision-making, including the anterior cingulate cortex (ACC), amygdala, insula, MFC, and OFC (Connolly et al., 2013; Yunker et al., 2021). Another report found that hypothalamic blood flow increased following NNS compared with NS intake in individuals with normal weight, whereas in individuals with obesity this effect was observed only relative to water and not NS (Chakravarti et al., 2025). In addition, hypothalamic FC following NNS ingestion varied with weight status. Individuals with normal weight exhibited stronger hypothalamic connectivity to cognitive regions, including the angular gyrus and superior frontal gyrus (SFG), whereas those with overweight or obesity showed weaker connectivity (Chakravarti et al., 2025), suggesting diminished top-down control over food-related behavior after acute NNS consumption. Furthermore, the only PET study included in this review found that BMI was associated with calorie-dependent dopamine changes, with lower dopamine release in individuals with obesity (Wang et al., 2014).

3.7.3. Metabolic state

Fifteen of the 21 reports were conducted in a fasted state. Three examined how metabolic state modulates responses to NNS and NS by directly comparing fasted and satiated conditions. In two reports,

hunger increased BOLD responses to sweet stimuli in gustatory and reward regions (e.g., insula, thalamus, and substantia nigra), whereas satiety enhanced activity in frontal and hippocampal regions, particularly for NS (Haase et al., 2009; van Rijn et al., 2015). In an additional analysis, van Rijn et al. (2016) showed that individual differences in reward sensitivity further modulated these responses. Participants with higher reward sensitivity exhibited stronger reward-related activity in response to NS versus NNS during satiety, even when calories were less needed (van Rijn et al., 2016). Conversely, during hunger, individuals with lower reward sensitivity exhibited this pattern, indicating that their reward signaling is closely linked to energy needs (van Rijn et al., 2016).

3.7.4. Habitual consumption of non-nutritive sweetener

Evidence on how regular NNS exposure influences brain responses is limited, as seven of the 21 included reports excluded habitual consumers to avoid confounding effects (Budzinska et al., 2024, 2025; Dalenberg et al., 2020; Griffioen-Roose et al., 2013; Stamataki et al., 2022; van Rijn et al., 2015, 2016). However, both extreme consumption and complete avoidance were excluded, as either pattern can influence reward sensitivity (Griffioen-Roose et al., 2013; Smeets et al., 2011; van Rijn et al., 2015, 2016). Only one report examined the effects of regular NNS consumption on brain responses during hedonic evaluation of acute NNS tasting, reporting greater reward-related activity in regular versus non-consumers, with higher caudate responses associated with lower weekly NNS exposure. In addition, only non-consumers showed differences in OFC activity between NNS and NS (Green & Murphy, 2012).

4. Discussion

This systematic review examined the effects of acute and short-term consumption of NNS-containing beverages on brain responses, as assessed in 20 fMRI and one PET report, and their relationship with appetite-related outcomes, including metabolic processes and eating behavior (Fig. 3). Brain and behavioral responses were influenced by intra- and inter-individual factors (e.g., sex, weight status, metabolic state, habitual NNS intake) and study design characteristics (e.g., dose, delivery method, sweetener type), likely contributing to inconsistencies and reduced confidence in the evidence.

4.1. Neural circuits underlying non-nutritive sweetener consumption

Sweet taste receptors on the tongue mediate oral gustatory signaling, transmitting sweet taste information to higher-order brain regions (Long et al., 2025). However, our systematic review suggests that sweetness paired with caloric content (NS) can elicit stronger activation in gustatory, somatosensory, and reward-related brain regions compared with sweetness alone (NNS). Although sweetness intensity was similar, pleasantness was higher for NS than NNS, a factor that has been linked to activity in the primary taste cortex (Frank et al., 2007) and to individual differences in brain responses (Budzinska et al., 2024, 2025). The energy value in NS may be more reinforcing than sweetness alone (de Araujo et al., 2020). The oxidation of glucose in peripheral tissues produces ATP, reflecting cellular energy availability (Weber et al., 2025). Post-oral nutrient sensing in the gut and hepatic portal system transmits

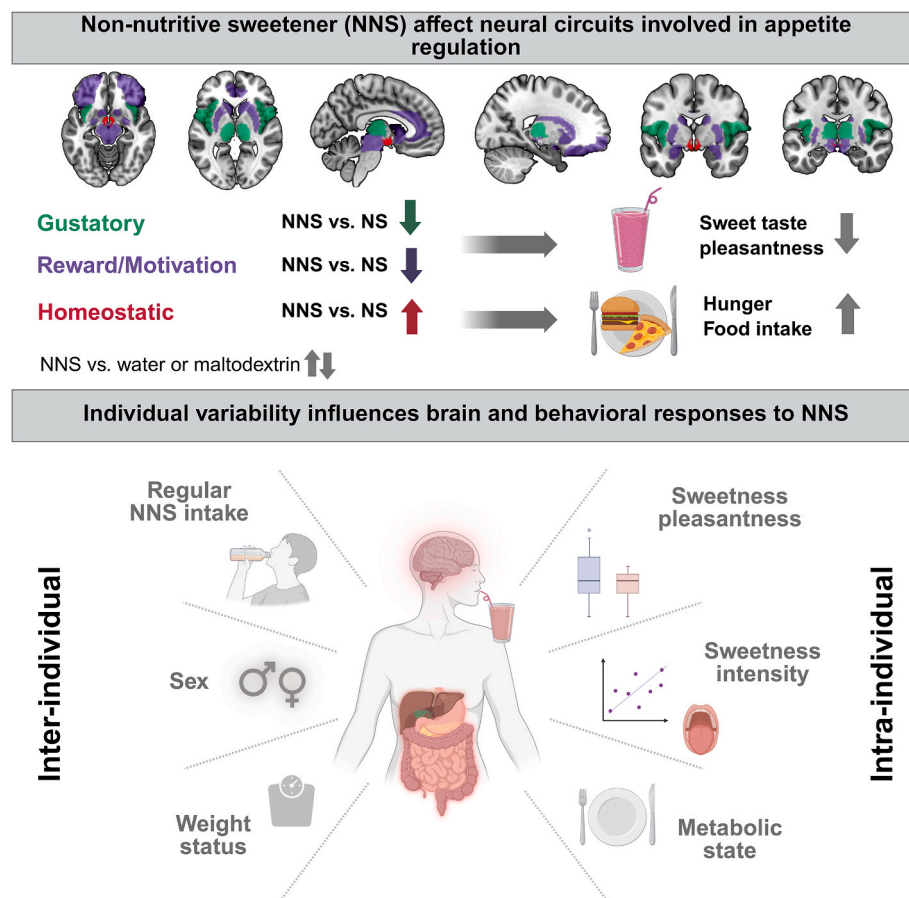


Fig. 3. Conceptual model of neural pathways implicated in the processing of non-nutritive sweeteners (NNS) based on findings from the systematic review. Brain regions are grouped in three functional circuits: gustatory (green: frontal and rolandic operculum, insula, thalamus), reward/motivation (violet: amygdala, anterior cingulate cortex, midbrain [substantia nigra/ventral tegmental area], medial and lateral orbitofrontal cortex, striatum [putamen, caudate, nucleus accumbens]), and homeostatic (red: hypothalamus). Brain and behavioral responses to NNS were influenced by inter- and intra-individual factors. Figure created with BioRender.com. Abbreviations: NS, nutritive sweetener; NNS, non-nutritive sweetener.

this information via vagal afferents to brain reward circuits, enhancing dopamine release independently of sweetness perception (Weber et al., 2025). This is consistent with the single PET study included in this review, which reported higher dopamine release after NS intake (Wang et al., 2014). Although responses to NNS appear lower than that observed for NS, reports also show increased activation in reward-related brain regions following NNS consumption compared with water (Budzinska et al., 2024, 2025; Farr, 2021; Meyer-Gerspach et al., 2022). In addition, one report found increased midbrain activity following water ingestion (van Opstal et al., 2019a), potentially driven by physiological effects of rehydration (Weber et al., 2025).

Most reports on post-ingestive effects of NNS versus NS focused on the hypothalamus (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022; Smeets et al., 2005a; van Opstal et al., 2019a; Yunker et al., 2021), due to its central role in energy homeostasis and nutrient sensing (for review, see (Wachsmuth et al., 2022)). Previous evidence consistently shows that glucose ingestion reduces hypothalamic activity, which is considered a neural marker of satiety (Luo et al., 2017; Smeets et al., 2005b, 2007; van Opstal et al., 2019b). Our findings for NS are consistent with this literature. The hypothalamus expresses sweet taste receptors, such as T1R2, enabling it to detect sweet taste from both NS and NNS (Jang et al., 2021). However, sweetness without calories may be associated with compensatory signals involved in the regulation of energy intake, as indicated by higher hypothalamic activity and FC following NNS compared with NS in three reports included in this review (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022; Smeets et al., 2005a). Since hypothalamic responses to glucose ingestion are dose-dependent (Smeets et al., 2005b), this raises the question of whether higher doses of sweetness-matched NNS may elicit stronger effects. In this review, reports using 75 g NS reported higher hypothalamic responses to NNS versus NS (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022; Smeets et al., 2005a), while a report using 50 g of various NS (fructose, glucose, sucrose) observed reduced hypothalamic activity across both NS and NNS (van Opstal et al., 2019a). Future studies should examine dose-dependent effects of NNS ingestion on homeostatic brain responses to clarify their implications for habitual dietary intake.

4.2. Effects of non-nutritive sweeteners on gut-brain axis and hormonal responses

Body-brain communication is a key mechanism in appetite regulation, mediated by the gut-brain axis to control food intake (Wachsmuth et al., 2022). Previous studies have shown that sugar alcohols can stimulate the release of gut hormones, including GLP-1, CCK, and PYY, and delay gastric emptying (Teyssie et al., 2022; Wölnerhanssen et al., 2016, 2021). In contrast, a previous review reported that artificial sweeteners do not induce gut hormone responses, indicating a reduced metabolic satiety signal (Ahmad et al., 2020). Consistent with this, our review also suggests that artificial NNS may elicit lower satiety-related hormonal responses than NS. However, evidence from neuroimaging reports remains limited and heterogeneous across different NNS types, with no observed associations with brain responses (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022).

4.3. Effects of non-nutritive sweeteners on glucose metabolism

NNS are commonly used in the dietary management of diabetes to reduce glycemic fluctuations (Moriconi et al., 2020). Overall, our review suggests that artificial NNS are comparable to water in their effects on glycemic responses, and that increases in blood glucose and insulin levels are driven by caloric content rather than sweet taste. Beyond the acute effects on glucose metabolism, the long-term consequences of NNS intake remain unclear. One report in this review reported impaired peripheral insulin sensitivity following two weeks of NNS intake combined with maltodextrin (Dalenberg et al., 2020). This was associated

with reduced reward-related brain responses to sweet taste (Dalenberg et al., 2020). This finding raises questions about how NNS interact with different food matrices, such as carbohydrate-rich meals, which more closely reflect real-world dietary conditions.

4.4. Effects of non-nutritive sweeteners on eating behavior and appetite outcomes

The sweet uncoupling theory proposes that sweetness without the expected caloric content may disrupt learned associations between sweet taste and energy intake. This mismatch between sweetness and energy may trigger compensatory responses following NNS compared with NS consumption (Egan, 2024), as suggested by two reports in our review that reported higher subjective hunger and food intake after NNS intake (Chakravarti et al., 2025; Yunker et al., 2021). Such effects would be contrary to the intended use of NNS in obesity prevention and management (Moriconi et al., 2020). However, these findings originated from the same study and should be interpreted with caution. Overall findings indicate no difference between NNS and NS in appetite-related outcomes, highlighting the need for further investigation into eating behavior and associated changes in brain activity. Since our review consistently found no significant differences in sweetness ratings between NNS and NS, sweetness matching appears to have been successful and is unlikely to account for the observed null or inconsistent findings. Nevertheless, several reports in this review suggest reduced reward-related brain responses and lower hedonic behavioral measures following NNS compared with NS consumption (Budzinska et al., 2024, 2025; Griffioen-Roose et al., 2013; Smeets et al., 2011; van Opstal et al., 2019a), consistent with sweet taste being less reinforcing in the absence of calories (de Araujo et al., 2020).

4.5. Impact of individual variability on non-nutritive sweetener responses

The inconsistent findings in this review may partly reflect individual variability. Some reports suggest that sex and weight status may influence brain and behavioral responses to NNS, with stronger homeostatic and reward-related responses observed in females and individuals with obesity (Chakravarti et al., 2025; Connolly et al., 2013; Yunker et al., 2021). Obesity is associated with altered neural circuits, such as reduced inhibitory control and heightened reward signaling (for review, see (Li et al., 2023)), which may explain differences in brain responses to acute NNS intake between individuals with obesity and those with normal weight. Future studies should investigate how sex and weight status interact to shape NNS-induced brain and behavioral responses. This may be particularly relevant for females with obesity, who may be more susceptible to food-seeking behavior influenced by sex hormones (Anversa et al., 2021). Since NNS are used as a dietary strategy in obesity management, habitual NNS consumption may also influence responses to NNS in individuals with obesity. However, this factor has rarely been investigated, with only one report in this review identifying an association between habitual NNS intake and reduced reward-related brain responses to sweet taste (Green & Murphy, 2012). Intra-individual factors such as metabolic state may further modulate brain responses to NNS. Specifically, fasting is associated with stronger activation of gustatory and reward-related regions in response to sweet taste (Haase et al., 2009; van Rijn et al., 2015, 2016), whereas satiety engages cognitive control and memory-related regions (Haase et al., 2009; van Rijn et al., 2015). Therefore, metabolic state should be considered when investigating responses to NNS, as consumption during hunger may potentially influence food cravings and eating behavior. Moreover, sweetness intensity and liking are associated with increased activity in homeostatic, reward-related, and gustatory brain regions (Budzinska et al., 2024, 2025; Frank et al., 2007; van Opstal et al., 2019a), supporting the role of sweet taste receptors in mediating these brain responses (Long et al., 2025). Since NNS are rated lower in sweetness liking compared with NS, this may contribute to the reduced activation

observed in gustatory and reward-related brain areas.

4.6. Limitations and methodological considerations

Substantial heterogeneity in study design, including differences in NNS type and dose, delivery timing, and administration method, limited comparability across the included reports. Most reports in this review investigated the acute effects of NNS intake on brain responses, whereas only a few examined short-term (Dalenberg et al., 2020; Tryon et al., 2015) or long-term NNS consumption and its effects on brain activity (Green & Murphy, 2012). This highlights the need for longitudinal studies to investigate the effects of regular NNS consumption on brain responses involved in appetite regulation. Sweetness matching across reports varied, with some using individual taste-based matching and others calculating sweetness based on relative sweetening power. This variability may contribute to differences in NNS doses and sweet taste signaling. Positive findings may reflect the high doses of NNS used in these reports (Chakravarti et al., 2025; Meyer-Gerspach et al., 2022; Smeets et al., 2005a; Yunker et al., 2021), which are not comparable to amounts found in typical diet beverages. Reports comparing NNS with water or maltodextrin demonstrated considerable variability in outcomes, underscoring the need for a standardized non-sweet control. Only one study used PET, whereas the remaining studies employed fMRI, making it difficult to draw conclusions about the involvement of specific neurotransmitter systems in response to NNS. Some findings should be interpreted with caution because they were derived from reports based on the same study but addressing distinct outcomes, which may limit the independence of evidence synthesis. No meta-analysis was conducted, as this was not feasible due to the heterogeneity of neuroimaging paradigms and analytical approaches across the included reports. Moreover, the review was limited by PICOS criteria to healthy participants and metabolic or behavioral outcomes assessed in neuroimaging reports, which may have restricted its scope. Although most included reports have focused on individuals with normal weight, investigating populations with overweight or obesity is crucial for public health.

4.7. Future directions and implications

The WHO does not recommend NNS as a substitute for reducing the high sugar intake common in Western diets, given the potential health concerns even when consumption remains within the acceptable daily intake (World Health Organization, 2023). Alterations in brain responses following acute and short-term NNS consumption raise the question of whether long-term use may also modulate appetite-related pathways. Longitudinal studies with larger and more diverse populations are needed to determine whether habitual NNS intake alters neural circuits underlying appetite regulation. Given that NNS are often used to reduce caloric intake and prevent glycemic spikes, further studies involving individuals with obesity and T2D are essential. This review indicates that individual variability shapes brain and behavioral responses to NNS, highlighting the need for future research to examine these differences more closely and inform personalized nutritional strategies. Inter-individual factors such as age and ethnicity may be important to consider in the context of NNS intake, particularly given the growing evidence that they can influence metabolic outcomes such as insulin resistance (AlShehab et al., 2025; Zhao & Yue, 2024). Most studies used high NNS doses in nutrient-free settings, which may limit external validity. Future research should reflect real-world conditions, in which NNS are typically consumed in lower doses with proteins, fats, or carbohydrates. Direct comparisons between artificial and naturally occurring NNS are needed to determine whether naturally occurring sweeteners provide a preferable option. Flavor modifiers may help attenuate homeostatic responses, as indicated by lower food intake (Gaider et al., 2025) and diminished hypothalamic activity (Ko et al., 2025).

5. Conclusion

Current evidence from human studies suggests that acute and short-term consumption of NNS-containing beverages modulates neural circuits involved in appetite regulation differentially than NS. Further investigation of NNS effects on the gut-brain axis is needed to understand the mechanisms underlying body-brain communication in appetite control. Individual factors, including sex, weight status, metabolic health, and habitual NNS consumption, appear to influence brain responses to NNS and may contribute to the heterogeneity of findings across reports. Interpretation is further complicated by heterogeneity in study design, participant characteristics, and analytical approaches. Experimental paradigms should reflect real-world conditions, including typical dietary doses and consumption within complex food matrices containing proteins, carbohydrates, and fats. Longitudinal studies in larger and more ethnically and demographically diverse populations are needed to clarify the long-term effects of NNS on the neural, behavioral, and metabolic mechanisms underlying appetite regulation and eating behavior. Such work could inform dietary guidelines and support more personalized nutritional recommendations that account for individual variability in response to NNS.

CRediT authorship contribution statement

Anja Bierenstiel: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Seohyeon Choi:** Writing – review & editing, Methodology, Investigation, Data curation. **Yoonsun Park:** Writing – review & editing, Methodology, Investigation, Data curation. **Leontine Sandforth:** Writing – review & editing. **Hubert Preissl:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Stephanie Kullmann:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **In-Seon Lee:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Ethical statement

Ethical approval was not required for this study, as it is a systematic review that synthesizes data from previously published studies involving human participants. No new data were collected.

Data availability

No new data were generated or analyzed in this study. This systematic review is based entirely on previously published studies, all of which are cited in the article.

Declaration of generative AI and AI-assisted technologies in the writing process

Generative AI tools (ChatGPT and DeepL Write) were used solely to assist with language editing and to improve readability during the preparation of the manuscript. All AI-assisted content was reviewed, and revised by the authors, who take full responsibility for the integrity and accuracy of the final text.

Funding

This review was conducted as part of an international collaboration and was supported by two funding sources: a grant (01GI0925) from the Federal Ministry of Research, Technology and Space (BMFTR) to the German Center for Diabetes Research (DZD), Tübingen, Germany, and a 2023 grant from Kyung Hee University (KHU-20233686), Seoul, Republic of Korea. The funders had no role in manuscript conceptualization, data curation, or other aspects of this work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.appet.2026.108803>.

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