NeuroImage 308 (2025) 121061

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Caloric labels do not influence taste pleasantness and neural responses to erythritol and sucrose

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ARTICLE INFO

Keywords:
Sucrose
Non-caloric sweeteners
Caloric labels
Implicit bias
fMRI
MVPA

ABSTRACT

Introduction: The beneficial effects of substituting sugar with non-caloric sweeteners (NCSs) remain uncertain due to the mismatch between their rewarding sweet taste and lack of energy content. Functional magnetic resonance imaging (fMRI) studies indicate an influence of cognitive processes (*e.g.*, beliefs, expectations) on reward system responses to NCSs, thereby changing their rewarding properties. We measured the impact of cognitive influences about the caloric content on brain responses and liking ratings to erythritol, a natural NCS with satiating properties, *versus* sugar (*i.e.*, sucrose).

Methods: We performed a within-subject, single-blind, counterbalanced fMRI study in 30 healthy males (mean ± SD: age 23 ± 0.6 years, BMI 22.5 ± 0.3 kg/m^2). Concentrations of erythritol were individually titrated to match the perceived sweetness intensity of a 16 % sucrose solution. During the scan, sucrose and equisweet erythritol solutions were delivered as 1 mL sips with either correct or purposefully incorrect "low-calorie" or "high-calorie" labels. After each sip, participants rated sweetness liking. Water with a "water" label was used as the control condition.

Results: A 2 × 2 ANOVA revealed lower liking ratings for erythritol than sucrose ($p < 0.0001$), but no main effect of the label, nor label-by-sweetener interaction. General Linear Model (GLM) analysis of brain responses at FDR $q < 0.05$ showed no main effect of sweetener nor label, nor a label-by-sweetener interaction. However, several patterns of brain activity mediated the differences in subjective liking ratings between the sweeteners. Moreover, different neural responses were found for *sucrose vs. water* in parcel-wise, SVM, and ROI-based analyses, whereas for *erythritol vs. water*, only the latter two showed differences. Lastly, sucrose induced a stronger craving signature response compared to erythritol, driven by the pattern specific to drug craving.

Conclusion: Liking ratings were lower for erythritol than sucrose, and they were unaffected by the caloric label. There were no differences in neural responses between the sweeteners and labels, except in comparisons with water.

1. Introduction

The replacement of sugar (*i.e.* sucrose) with non-caloric sweeteners (NCSs) has become a common strategy to decrease high sugar consumption and the risk of developing numerous non-communicable diseases, in particular metabolic disorders such as obesity and type 2

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https://doi.org/10.1016/j.neuroimage.2025.121061
Received 13 August 2024; Received in revised form 26 January 2025; Accepted 27 January 2025
Available online 28 January 2025

diabetes mellitus (Johnson, 2013). Different categories of NCSs exist, with artificial sweeteners such as sucralose, aspartame, acesulfame-K, and saccharine being the most widely used (Sylvetsky, 2016). Artificial NCSs contain little or no calories and retain a sweet taste while having no or little effect on glucose homeostasis (glucose and insulin concentrations) (O'Connor, 2021). However, despite a considerable increase in their commercial use and consumption, the beneficial effects of replacing sugar with NCSs on long-term energy intake and body weight remain debatable (Toews, 2019; Rogers, 2021; McGlynn, 2022). This uncertainty is often attributed to the mismatch between the sweet taste of NCSs (rewarding oral effect) and their lack of energy content (lack of post-ingestive satiating effect), which may result in compensatory overeating in terms of meal size and/or frequency (O'Connor, 2021).

Erythritol is a NCS that belongs to the naturally occurring polyols. It contains no calories and does not impact glucose or insulin concentrations (Livesey, 2003), but unlike artificial NCSs and similar to glucose and sucrose, erythritol stimulates the release of anorexigenic gastrointestinal (GI) hormones [cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY)] modulating satiation (Overduin, 2016; Sorrentino, 2020; Wölnerhanssen, 2016; Teysseire, 2022). Moreover, we previously showed that neural responses to the taste of erythritol and sucrose in taste, reward, and homeostatic regions did not differ (Budzinska, 2024). However, perceived taste pleasantness was lower for erythritol than for sucrose. Hence, more research is needed to further evaluate erythritol's potential as a promising sugar alternative.

Another strategy that is increasingly being used to promote healthy eating is the provision of nutritional information on food and beverage packaging through food labels or nutrition claims (Prada, 2021; Rramani, 2023). While the primary goal of such information is to help consumers identify and choose healthier options (Kaur, 2017; Talati, 2017; WHO, 2011), their influence on consumers' expectations and perceptions sometimes leads to unintended effects (*e.g.* increasing consumption or misjudging other potentially less healthy food aspects) that can compromise their overall effectiveness (Oostenbach, 2019). For instance, food labels can significantly influence taste pleasantness, with labels indicating lower caloric content often leading to reduced expected, and sometimes perceived, taste pleasantness (Levin, 1988; Ng, 2011; Norton, 2013; Okamoto, 2013; Piqueras-Fiszman, 2015). This phenomenon is likely driven by cognitive biases and consumer expectations, which typically associate higher caloric content with better taste. In addition, food labels have been shown to significantly impact neural responses in brain areas implicated in taste and reward processing, as well as levels of metabolic hormones in response to food stimuli. For example, Crum et al. showed a decrease in ghrelin concentrations after consuming a drink that participants believed to be highly caloric, even though it had the same amount of calories as the drink introduced as low-caloric (Crum, 2011). Other studies showed differential neural responses in the midbrain, hypothalamus, and ventromedial prefrontal cortex (vmPFC) when comparing neural responses to isocaloric drinks presented with opposite health-related labels ("healthy" *vs.* "treat" or "low-fat" *vs.* "high-fat") (Veldhuizen, 2013; Ng, An fMRI study of obesity, food reward, and perceived caloric density. Does a low-fat label make food less appealing?, 2011). Lastly, also price labels have been shown to impact subjective liking and neural responses in the medial PFC (mPFC) to the taste of wine, further highlighting important top-down modulation of reward responses by cognitive processes that encode flavor expectancies (Plassmann, 2008). However, despite the growing use of erythritol in many food products, research on the impact of food labels on perceptual and neural responses to its taste is still completely lacking.

Therefore, the present study aimed to investigate the influence of caloric labels on taste pleasantness (*i.e.* subjective liking) as well as neural responses to erythritol *versus* sucrose. To improve transparency and reduce bias, we preregistered our specific objectives and hypotheses together with the data analysis plan on the OSF platform.

Our *first objective* was to study potential differences in taste pleasantness (*i.e.* subjective liking ratings) to oral administration of *erythritol vs. sucrose*, depending on the caloric label. Given the mixed findings of previous studies, including the lack of effect of health-related labels (Veldhuizen, 2013; Wegman, 2018; Bialkova, 2016; Rramani, 2023), but a significant influence of a price label (Plassmann, 2008) on subjective liking ratings, we refrained from formulating specific hypotheses for the main effect of caloric label as well as the label-by-sweetener interaction effect. For the main effect of sweetener, we hypothesized lower subjective liking ratings for erythritol compared to than for sucrose, based on our previous results (Budzinska, 2024). Similar to the main effect of label, we refrained from formulating specific hypotheses for the label-by-sweetener. Our *second objective* was to study neural responses to *erythritol vs. sucrose* in the taste cortex, reward, and homeostatic regions, depending on the label. For the main effect of label, we hypothesized i) no effect of caloric label on neural responses in the taste cortex (Veldhuizen, 2013; Plassmann, 2008; Grabenhorst F. S., 2013), ii) increased neural responses to a "*high-calorie" vs. "low-calorie*" label in brain reward regions, regardless of the sweetener (Veldhuizen, 2013; Plassmann, 2008), and iii) greater deactivation of the midbrain and hypothalamus to "*high-calorie" vs. "low-calorie*" label, as Veldhuizen *et al.* described these areas as sensitive to the modulating effects of external cues (Veldhuizen, 2013). For the main effect of sweetener, we hypothesized no differences in neural responses to *erythritol vs. sucrose* in any of the taste, reward and homeostatic regions, based on the lack of significant differences in neural responses in our previous study (Budzinska, 2024). For the label-by-sweetener interaction effect on neural responses, we refrained from formulating specific hypotheses due to the lack of studies that investigated the interaction between caloric labels and sweet substances. In case of significant findings for the main effect of label, our *third (exploratory) objective* was to study the differences in the strength of reward system functional connectivity between the caloric labels, independent of sweetener. Lastly, the *fourth (exploratory) objective* was to explore in which brain regions neural responses predict sweetness liking ratings across conditions.

2. Methods

2.1. Sample and study design

The study employed a within-subject, single-blind, counterbalanced design. Healthy male adults were recruited through the flyers distributed at KU Leuven University buildings and social media. Subjects who spoke either Dutch and/or English were eligible. The inclusion criteria were: (i) age 20–40 years, (ii) body mass index (BMI) 18.5–25 kg/m^2, (iii) stable body weight for at least three consecutive months at the start of the study, (iv) right-handedness. The exclusion criteria were: (i) any current or previous medical, gastrointestinal, or psychological condition, (ii) current or recent regular medication use, (iii) smoking, (iv) high caffeine intake ($>$ 1000 mL coffee daily or equivalent), (v) alcohol dependence or abuse ($>$ 2 units per day/14 units per week), (vi) use of cannabis or any other drug of abuse during the 6 months prior to the study, (vii) night-shift work, (viii) emotional and/or restraint eating behaviour, (viii) regular use of NCS products ($>$ 1 a week), ix) food allergies and/or fructose intolerance, (x) regular intake of energy drinks ($>$ 1 energy drink a day), (xi) supertaster status as determined in a PROP (6-n-propylthiouracil) sensitivity test (Bartoshuk, 2004), (xii) claustrophobia, severe back problems or other interfering contraindications for the MRI exam.

The study was approved by the Ethics Committee Research UZ/KU Leuven (S65927) and performed according to the latest version of the WMA Declaration of Helsinki (2013). Prior to the study's initiation, each participant provided both verbal and written informed consent.

2.2. Study procedures

The study consisted of a total of two visits within a maximum of 12 days (Fig. 1). In addition, participants were instructed to refrain from alcohol and excessive exercise one day prior to the experiment. At the start of each visit, appetite-related sensations such as hunger, appetite, fullness, satiation, prospective food consumption, and nausea were measured using Visual Analogue Scales (VAS).

2.2.1. Screening and sweetness matching visit (Study visit 1)

At the beginning of study visit 1, participants were screened for in- and exclusion criteria using an interview and several validated questionnaires which are described in *Supplement*.

We also performed a PROP sensitivity test to ensure participants were not supertasters who tend to give heightened responses to a broad range of oral stimuli, thereby impairing between-subjects comparisons (Tepper, 2001). During the test, participants drank 10 mL of 0.1 mol/L NaCl and 0.32 mmol/L PROP solutions and rated their intensity on the General Labelled Magnitude Scale (gLMS) ranging between 0 (no sensation) and 100 (strongest sensation of any kind), including intermediate labels. In case of a score of more than 50 for the PROP solution, indicating supertaster status, subjects were not allowed to participate in the study.

Eligible participants were trained on the use of the General Intensity Scale (GIS) to measure perceived sweetness intensity throughout the study (0:100, no sensation to strongest sensation of any kind) (Kalva, 2014). Afterwards, we performed sweetness matching to individually match the erythritol and sucrose solutions for perceived sweetness intensity, as well as a triangle test to check whether participants were able to discriminate the two sweet solutions. The sweetness matching and triangle test procedures were as described in detail in our previous stud (Budzinska, 2024) Briefly, participants consumed 2 mL of sucrose and erythritol solutions across a range of concentrations and rated their perceived sweetness intensity on the GIS, to establish individual dose-response relationships for the two sweeteners. We then determined the concentration of erythritol solution matched to the perceived sweetness of a 16 % sucrose solution for each participant individually based on the fitted dose-response sigmoidal curve (Wee, 2018) The 16 % sucrose concentration was chosen as a reference based on the sweet taste concentrations used in the majority of studies reviewed by Roberts (2020), as well as findings from our previous study, where a lower reference concentration was used, and overall liking ratings were relatively low (Budzinska, 2024). We then conducted a triangle test using both the 16 % sucrose and individually matched equisweet erythritol solutions. Throughout the visit, 10 mL of tap water was given for rinsing after each 2 mL sweet solution to avoid taste saturation.

2.2.2. fMRI scan (Study visit 2)

Data were acquired on a 3T Philips Achieva DStream MRI scanner with a 32-channel head coil within the Radiology Department of the University Hospitals Leuven. All scans took place between 8 and 12AM. Before the fMRI scan, participants tasted the 2 equisweet solutions again as well as water and rated their perceived sweetness intensity with the GIS to check for potential changes in perceived sweetness intensity compared to the 1st visit. They also rated provided their ratings on the General Hedonic Intensity Scale (GHIS), ranging from –100 to 100, to measure the subjective pleasantness (*i.e.* liking ratings) of the solutions containing different sweeteners and water. A baseline glucose measurement was collected prior to scanning to check the fasting state. fMRI acquisition was conducted with a multiband EPI acquisition sequence (60 transverse slices; TE = 30 ms, flip angle = 90°; field of view = 224 (RL, AP), 132 (FH); TR = 1.8 s, 2 × 2 × 2 mm^3 voxels) in a single-blind, counterbalanced long event-related fMRI paradigm consisting of 6 runs of 15 trials each (5 conditions x 3 repetitions) (Fig. 2). The five conditions included 1) sucrose with "high-calorie" label, 2) sucrose with "low-calorie" label, 3) erythritol with "high-calorie" label, 4) erythritol with "low-calorie" label, 5) water with "water" label (control condition). One trial consisted of the simultaneous presentation of a visual cue with either "high-calorie" or "low-calorie" label and the oral delivery of 1 mL of one of the two sweet solutions (each solution was correctly labelled and mislabelled), or with the presentation of the label "water" and delivery of 1 mL of water. The delivery and label presentation lasted 4 s and was followed by a jittered interval (between 7 and 11 s), a swallowing cue (4 s), delivery of 1 mL water to rinse (4 s), again swallowing cue (4 s), sweetness liking ratings (6 s) using the GHIS, and an intertrial interval (9 s). Thus, the whole trial duration was 31 s, the run duration was 11 min, and the total scan duration 71 min.

The data is available as Brain Imaging Data Structure (BIDS) dataset in the BIDS repository within the "super repository" for this study on G-Node Infrastructure (GIN).

2.3. Data analysis

2.3.1. Preregistered analyses

The 1st and 2nd preregistered analysed aims comprised the comparison of the subjective liking ratings collected during each trial as well as brain BOLD responses to *erythritol vs. sucrose*, depending on the presented caloric label. The 3rd aim concerned potential differences in reward system functional connectivity between the caloric labels, independent of the solutions, and the 4th one included predictive modelling of the sweetness liking ratings based on the neural responses across the sweet-tasting conditions (both labels and both sweeteners, without water).

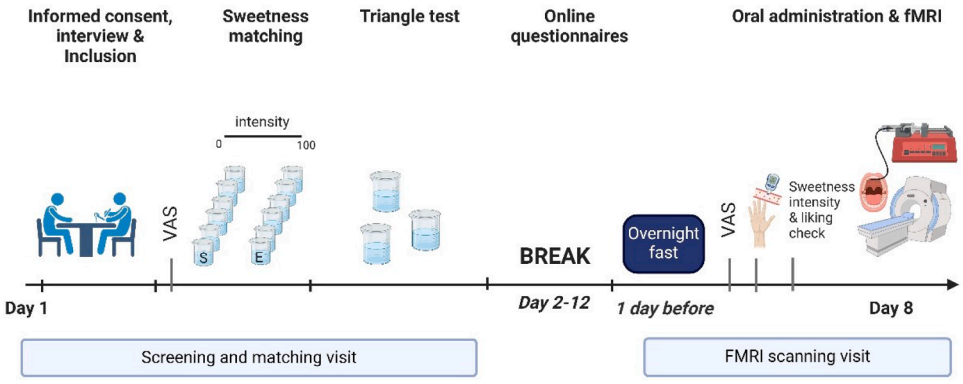

Fig. 1. Overview of the two study visits: (i) screening and sweetness matching visit, consisting of screening, sweetness matching, and triangle test, (ii) fMRI scanning visit. Participants were fasted at the start of each visit, which started with the collection of appetite-related sensations using VAS. Before the scan, we measured capillary blood glucose levels, and participants rated the sweetness intensity and liking of the two sweeteners and water using the GIS (0:100) and GHIS (−100:100). fMRI, functional magnetic resonance imaging, VAS, Visual Analogue Scale, GIS, General Intensity Scale, GHIS, General Hedonic Intensity Scale.

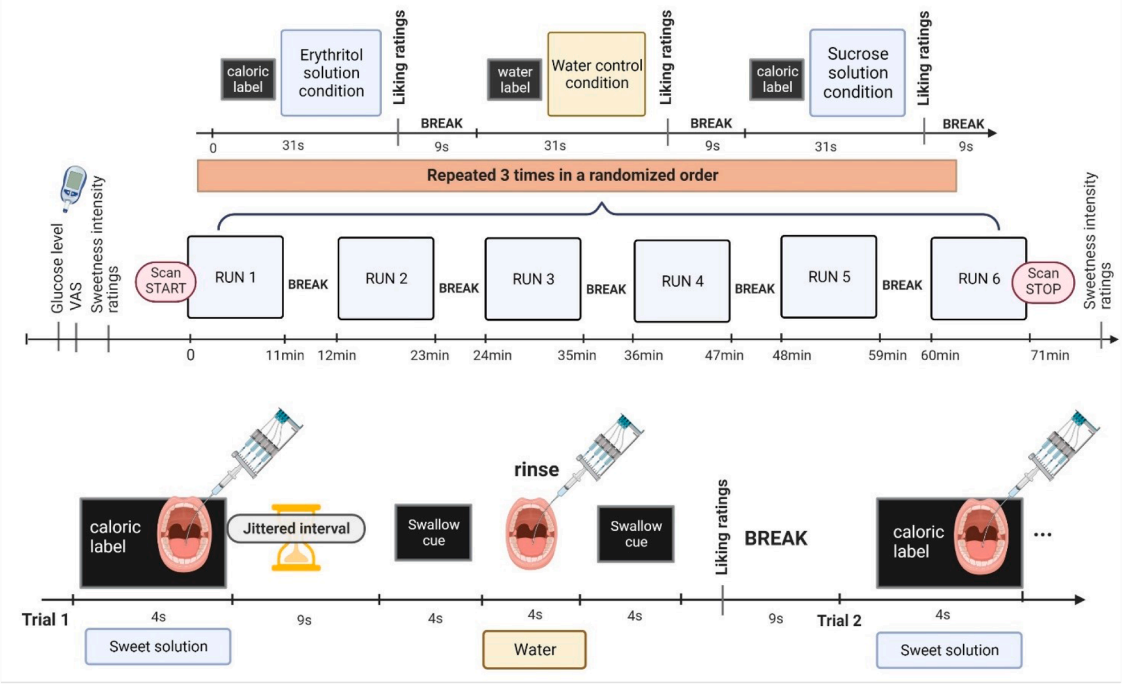

Fig. 2. fMRI design. The fMRI scan consisted of six runs of 15 trials each (5 conditions repeated three times) in counterbalanced order. The total run and scan durations were 11 and 71 min, respectively. Each trial started with a delivery of one of two solutions (sucrose, erythritol) with one of two labels (low-, high-calorie), or water (with water label), followed by a jittered interval during which the solution was kept in the mouth, swallowing cue, delivery of water to rinse the mouth, swallowing cue, and presentation of GHIS scale to rate the delivered solution (−100: 100). After the 9 s break, the next trial started.

2.3.1.1. Behavioural data analysis. The SAS code used to analyze the behavioural data is in the code GIN repository.

The trial-by-trial online subjective sweetness liking ratings constituted the primary outcome variable. To analyze this, we conducted a 2 (*sweetener*) x 2 (*label*) within-subject ANOVA implemented in a linear mixed model framework in SAS 9.4 software (SAS Institute, Cary, NC, USA). This approach allowed us to test the main effects of "*sweetener*" and "*label*" (both categorical, 2 levels, within-subject), as well as their two-way interaction on these ratings. Moreover, putative time (*i.e.* repetition) effects were explored by adding "*trial number*" as a continuous covariate (fixed effect) to the 2 × 2 ANOVA, including its interaction with the two factors ("*sweetener*", "*label*") and the 3-way "*label-by-sweetener-by-trial number*" interaction. The main effect of "*trial number*" explored linear trends in liking ratings over time, whereas the interactions explored whether these linear trends differed between the conditions. Random intercepts and random trial number slopes (centred around the mean) were fitted for each participant, and a Kronecker product covariance structure was used to model the correlations within participants between conditions and time points, with an unstructured and a first-order autoregressive structure, respectively. Akaike's Information Criterion (AIC) was used to select the best-fitting model. Following model estimation, we tested the main effects of sweetener, label, and their interaction, followed up with pairwise comparisons between erythritol and sucrose, high- and low-calorie labels, and the label-by-sweetener interactions.

In addition, we compared the pre-scan sweetness intensity ratings for erythritol and sucrose using a marginal linear mixed model. Subsequently, in two additional analyses, we examined whether adding these sweetness intensity ratings as well as hunger ratings as covariates to the model analysing sweetness liking ratings had an impact on the observed differences between the conditions. We focused on the influence of hunger given its high correlation with the other appetite-related sensations. Moreover, among these variables, hunger has been consistently identified in the literature as significantly impacting outcomes in research comparing caloric with low-caloric versions of various taste stimuli (Haase, 2009; Nolan-Poupart, 2013).

Finally, calculations of subjects' perceptual ability to discriminate the equisweet solutions of erythritol and sucrose in the discrimination task (*i.e.* triangle test) are described in *Supplement.*

2.3.1.2. GLM analyses of brain BOLD responses. Details on fMRI data pre-processing and quality control (QC) are in *Supplement.* No signal dropout was identified using available QC measures.

2.3.1.3.0. First-level analyses. fMRI data were analysed at the first (*i.e.* subject) level by the general linear model (GLM) using custom Matlab scripts (included in the code GIN repository) based on template scripts in the LaBGAScore Github repository calling SPM12 (Statistical Parametric Mapping) routines as well as functions from the CanlabCore toolbox. The five conditions (high-calorie labelled sucrose, low-calorie labelled sucrose, high-calorie labelled erythritol, low-calorie labelled erythritol, water-labelled water) were modelled as 'long events' corresponding to the duration of label presentation, solution delivery and keeping it in the mouth. The first-level design matrix included one regressor of interest for the response to each condition, as well as nuisance regressors: (1) two regressors modelling the water rinsing and swallowing phase, as well as rating phase; (2) one regressor for the average CSF signal representing physiological noise; (3) 12 head motion parameter regressors, and (4) one regressor per spike volume defined based on the head motion parameter thresholds mentioned in *Supplement.* Run intercepts were included as well. Residual temporal autocorrelation in the BOLD signal was addressed by fitting a first-order autoregressive (AR1) model to the residuals of the regression model with consecutive pre-whitening of the data. This way of first-level GLM modelling was found to fit best to our data based on Bayesian Model Selection on the data of our previous study with a very similar design (Budzinska, 2024)

The following eight first-level contrasts were created: each of the five conditions *vs.* implicit baseline; high-calorie labelled sucrose and erythritol *versus* low-calorie labelled sucrose and erythritol (main effect of label), high- and low-calorie labelled sucrose *versus* high- and low-calorie labelled erythritol (main effect of sweetener), interaction of

label and sweetener. The latter three contrasts were our primary contrasts of interest, while the remaining ones were added for interpretation purposes.

The results of the first-level analysis are available in the first-level GIN repository for this study.

2.3.1.4.0. Second-level analyses. fMRI data were analysed at the second (*i.e.* group) level by the GLM implemented in custom Matlab scripts (included in the code GIN repository) based on template scripts in the LaBGAScore and CANlab_help_examples (LaBGAS fork) Github repositories calling SPM12 (Statistical Parametric Mapping) routines as well as functions from the CanlabCore toolbox. The default SPM threshold for including voxels was adjusted from 80 % to 20 % of the global mean to prevent unnecessary exclusion of relevant voxels in the analyses.

To address our 2nd preregistered aim, the second level analysis assessed neural responses within a mask of predefined regions that consisted of 125 brain parcels merged from the Canlab 2018 combined atlas and the California Institute of Technology (CIT168) probabilistic high-resolution *in vivo* atlas of subcortical areas (Pauli, 2018)(*Supplementary Table 1*). The selected regions corresponded to those included in our previous study (Budzinska, 2024), and included the primary taste cortex [mid-insula (MI), anterior insula (AI), frontal operculum (FO)], reward processing regions (precentral gyri, thalamus, midbrain (ventral tegmental area (VTA), substantia nigra (SN)), striatum, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), amygdala, hippocampus), as well as the hypothalamus and brainstem (medulla, various nuclei) involved in the homeostatic regulation of food intake.

A group-level mass univariate robust voxel-based GLM on the three first-level primary contrasts of interest (main effect of sweetener, main effect of label, label-by-sweetener interaction) was performed by entering the parameter estimate (*i.e.* beta) images from the designated first-level contrasts into a second-level random-effects analysis. Further, in four additional contrasts we also compared the respective sweeteners (sucrose across both caloric labels, erythritol across both caloric labels), and labels (high-calorie labelled sucrose and erythritol, low-calorie labelled sucrose and erythritol) *vs.* water for interpretation purposes. In total, the second-level analysis consisted of seven contrasts, three to test our primary hypotheses and the remaining ones for interpretation. Equivalent contrasts were calculated for the mean liking ratings for each condition, creating delta (Δ)-liking ratings which were added as covariates to the final 2nd level design matrix to control for potential differences in subjective liking, as preregistered.

We complemented these voxel-based analyses with parcel-wise robust GLM analyses in our mask of 125 parcels using the robfit_parcelwise function in the CanlabCore toolbox. Both analyses were thresholded at $q_{FDR}<0.05$.

Finally, we also performed individual region of interest (ROI)-based robust GLM analyses in 7 key regions divided into 3 distinct groups of brain areas shown in *Supplementary Fig. 1* and *Supplementary Table 2*. These groups included: 1) taste cortex constituting insular cortex (MI+AI) and FO, 2) reward areas consisting of ventral striatum (NAc), dorsal striatum (caudate, putamen), VTA/SN, medial and lateral OFC, and 3) hypothalamus.

To study the brain mechanisms explaining potential differences in sweetness liking ratings between conditions, we performed whole-brain multivariate mediation analyses using the principal directions of mediation (PDM) method (Geuter, 2020) implemented in the Canlab Mediation Toolbox. Our custom scripts can be found in the code GIN repository. Due to the lack of differences between the caloric labels (see *Results 3.2.1.b Sweetness liking ratings*), the contrast testing the main effect of sweetener constituted the independent variable 'x, the dependent variable 'y' was the respective difference in sweetness liking ratings, and the mediator 'm' was the respective whole-brain neural response to this contrast. This approach decomposes the neural activity across the whole brain into orthogonal networks that mediate the main effect of sweetener on subjective liking ratings.

2.3.1.5. Functional connectivity analyses. The 3rd preregistered aim was an exploratory aim that investigated whether functional connectivity between the seeds (*i.e.* brain regions showing significant differential activation for the main effect of label) and other regions from the mask differed between the high- and low-calorie label, independent of sweetener. However, due to the lack of significant findings for the contrast testing the main effect of label, we did not pursue further analysis of this objective.

2.3.1.6. Predictive modelling of individual liking ratings from brain activation patterns. To address our 4th preregistered aim, we performed whole-brain Multivariate Pattern Analysis (MVPA) (Nolan-Poupart, 2013), with details provided in Supplement.

2.3.2. Additional analyses

2.3.2.7. Bayesian GLM. Analogous to our previous study, we also complemented the frequentist second-level GLM analysis within the mask of regions with a Bayesian GLM analysis to evaluate the relative support in favour of the null *vs.* alternative hypothesis (Soch, 2018; Budzinska, 2024). We selected a threshold of $0.0333 > BF > 10$ indicating strong evidence in favour of the null or alternative hypothesis, respectively (Rouder, 2009). We implemented this analysis using the estimateBayesFactor function from the CanlabCore toolbox, which converts statistic images (in this case, t maps) to maps of (log) Bayes Factors.

2.3.2.8. Support vector machine classification. In addition to mass univariate GLM analyses, we used support vector machines (SVM) as a (binary) MVPA classification algorithm to test whether the solutions (both sweeteners and water) or labels (both caloric labels and water label) can be correctly classified based on their whole-brain response patterns. Detailed methods are provided in the Supplement.

2.3.2.9. Neurobiological pleasure and craving signatures. Lastly, considering the emergence of multivariate predictive brain models that allow prediction of an individual person's mental state or behaviour (outcomes) based on their patterns of brain activity (Kragel, 2018), we quantified the expression of the recently discovered fMRI-based multivariate signatures predicting behavioural measures of pleasure (Kragel, 2023) and craving (Neurobiological Craving Signature, NCS (Koban, 2023). These brain signatures are distributed patterns of fMRI responses, defined previously in independent datasets by MVPA, which sensitively and specifically track subjective pleasure and self-reported intensity of cue-induced drug and food craving, respectively. The strength of the signature responses was estimated using the dot product calculation of the beta weight of the respective condition/contrast activation maps specified in the 1st level analyses and the signature maps. This process yields scalar pattern expression values for each subject.

3. Results

3.1. Sample size

Thirty healthy male participants with an average age of 23.0 ± 0.6 years old and body mass index (BMI) of 22.5 ± 0.3 kg/m^2 were included. There were no dropouts between the two study visits (of which only one was an fMRI visit). However, two participants were excluded due to excessive movement during fMRI scanning. To reach the intended sample size, we replaced these participants by recruiting two additional subjects. Several previous studies have investigated the effect of nutrition labels on food valuation in the brain using similar experimental study designs (Grabenhorst, 2013; Plassmann, 2008; De Araujo, 2005). Although so far, no other study investigated the effect of such cognitive manipulation on subjective pleasantness or neural responses to the taste

of erythritol, there are similar experiments that used other sweeteners (Wegman, 2018; Veldhuizen, 2013). Moreover, previous data on effect sizes of cognitive modulation of consummatory taste in fMRI studies are completely lacking, but a power calculation indicated that a sample size of $N = 30$ yields 80 % power to detect a small effect size ($f = 0.21$) in the omnibus test of the 2 × 2 within-within ANOVA testing differences in brain responses.

3.2. Preregistered analyses

3.2.1. Behavioural analyses

Behavioural data are reported as estimates and standard error (SE) derived from the statistical analysis.

3.2.1.10. Sweetness matching and intensity ratings. Based on the perceived sweetness intensity of a 16 % sucrose solution, the average erythritol solution concentration across participants was μ=17.3 ± 1.0 % (min=7.2 %, max=29.2 %). Despite the great inter-individual variability in subjective sweetness intensity sensitivity (Fig. 3), pre-scan intensity ratings to the 16 % sucrose (41.2 ± 3.9) and matched erythritol (μ=45.2 ± 3.9) solutions did not differ significantly (*erythritol vs. sucrose:* $t(29) = -1.20$, $p_{uncorrected}$=0.24). This was further supported by a Bayesian *t*-test indicating moderate evidence in favour of the null rather than alternative hypothesis (BF_{10}=0.37). The average water intensity rating was μ=6.72±1.72.

Although we carefully matched sweetness intensity levels, the majority ($n = 21$, 70 %) of participants could still differentiate the erythritol and sucrose solutions above chance level in the discrimination task (*i.e.* triangle test), regardless of the combinations. Detailed results are provided in *Supplement*.

3.2.1.11. Sweetness liking ratings. A total of 18 liking ratings per condition were collected throughout the scan using the GHIS. Average group-level liking ratings per condition are presented in Fig. 4 panel A; average subject-level liking ratings per condition can be found in Fig. 4 p*anel B*. The distribution of liking ratings for each participant and for each condition is shown in *Supplementary Fig. 2*. Since water was rated as neutral (μ=0.92±0.36) and it served as a control, water ratings were not included in the primary analyses of interest. We found a significant main effect of sweetener (F(1355)=49.17, $p < 0.0001$), with significantly lower liking ratings for erythritol (μ=17.56±3.00) than for sucrose (μ=24.68±3.00, $t(355) = -7.01$, $p < 0.0001$, Fig. 4 panel *C*). Despite this significant main effect at the group level, we did observe considerable variability in liking ratings to erythritol and sucrose (across both labels, showing the main effect of sweetener) between participants (Fig. 4 *panel D)*. Further, there was no significant main effect of label, nor label-by-sweetener interaction (F(1219)=0.93, $p = 0.33$; and F(1, 214)=0.24, $p = 0.63$ respectively). Notably, the main effect of trial repetition (*i.e.* time) was also non-significant ($F(1, 415)=0.95$, $p = 0.52$), nor was there an interaction of trial repetition with any of the other effects, indicating that there was no linear trend (*i.e.* habituation or sensitization) in liking ratings over trials/time, and that this also did not differ between conditions.

Consistent with our previous study (Budzinska, 2024), higher sweetness intensity ratings were significantly associated with higher liking ratings ($F(1, 356)=62.24$, $p < 0.0001$, μ=0.39±0.04), and the interaction between intensity and sweetener was not significant ($F(3, 162)=1.28$, $p = 0.28$). This indicates a consistent positive association of intensity and liking ratings for both sweeteners, regardless of the caloric label. Adjusting for intensity did not impact any of the findings, with a significant main effect of sweetener (μ=25.36±2.74 for sucrose, μ=16.68±2.74 for erythritol, $t(355) = -9.03$, $p < 0.0001$), and no significant effects of label ($p = 0.32$) or label-by-sweetener interaction ($p = 0.62$) on sweetness liking ratings.

Lastly, hunger ratings collected prior to scanning were not associated with sweetness liking ratings($F(1, 27.5)=0.06$, $p = 0.80$) when included in the model as a covariate.

3.2.2. Differences in brain BOLD responses between the sweeteners

The results of the *voxel-wise* GLM analyses at $q_{FDR} < 0.05$ within the mask of regions revealed no significant differences for any of the 2nd level primary contrasts of interest (main effect of label, main effect of the sweetener, label-by-sweetener interaction), nor for any of secondary contrasts (*erythritol vs. water* and *sucrose vs. water*). Given the lack of significant effect of caloric label in both the behavioural and brain BOLD GLM analyses, the results of the contrasts between each caloric label *vs.* water are not reported as these contrasts merge the effects of erythritol and sucrose when comparing the high- and low-caloric labels with water.

Likewise, in our *parcel-wise* analyses, we observed no significant differences for any of the primary contrasts of interest (main effect of sweetener, main effect of label, label-by-sweetener interaction). In the secondary contrasts, we found no significant differences for *erythritol vs. water*. However, *sucrose vs. water* did show significant activations in the amygdala, putamen, nucleus accumbens (NAc) (ventral striatum), (ventral) pallidum, sublenticular extended amygdala (SLEA), hypothalamus, hippocampus, subiculum, bilateral MI, FO, posterior insula (PI), subgenual anterior and subcallosal cingulate cortex (sgACC, SCC), anterior midcingulate cortex (aMCC), inferior frontal gryus (IFG),

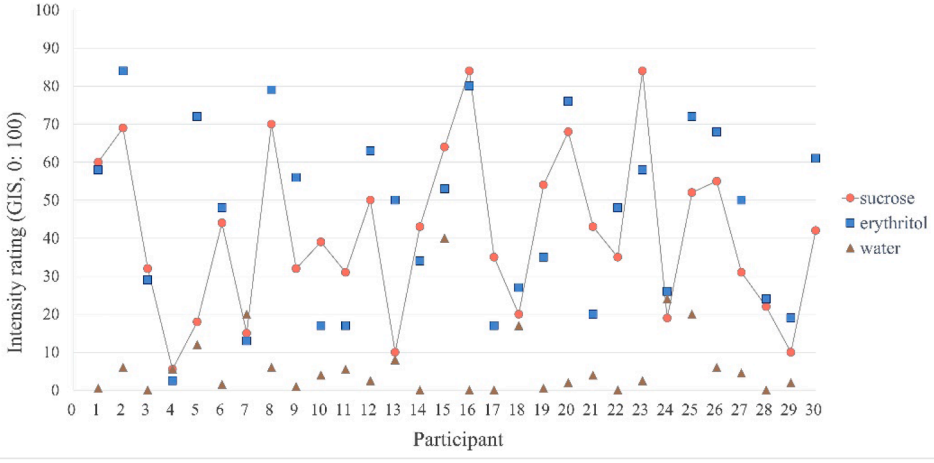

Fig. 3. Individual pre-fMRI intensity ratings for sucrose and erythritol on the GIS (0:100). The green continuous line corresponds to the 16 % sucrose solution and the red triangles to water (control).

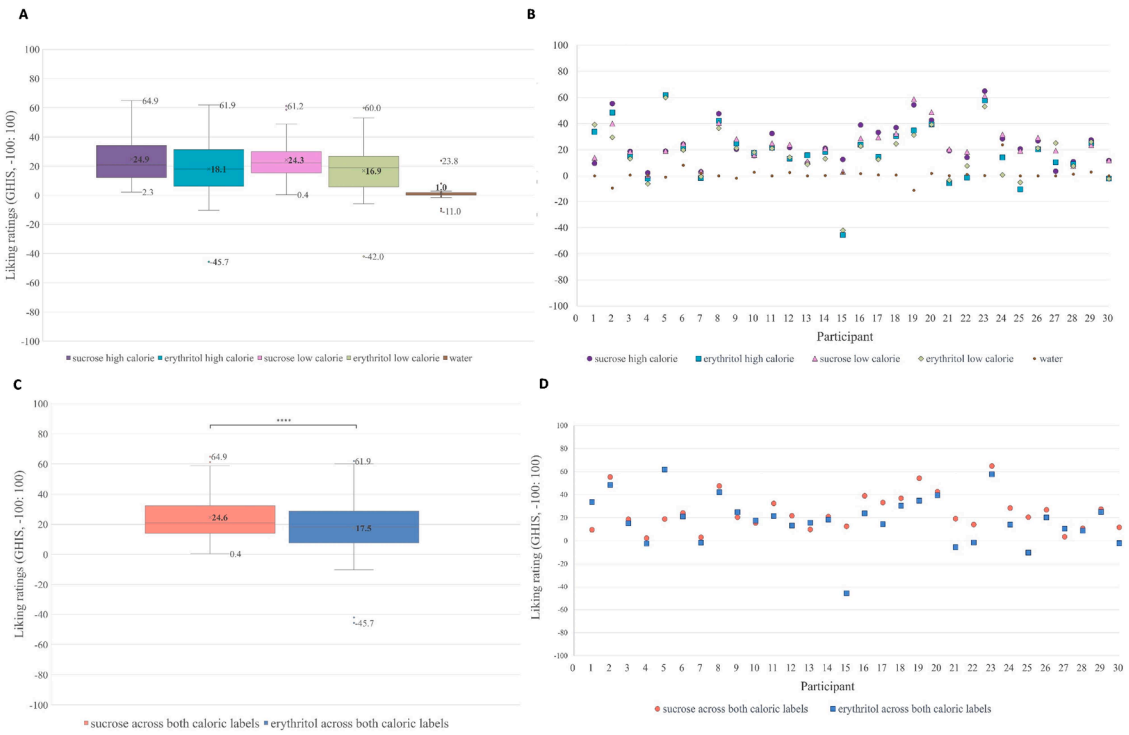

Fig. 4. Average GHIS liking ratings. Numbers correspond to the mean, minimal and maximal values.
A: Group-level sucrose and erythritol for all the conditions with their respective caloric label. B: Individual sucrose and erythritol for all the conditions with their respective caloric label. GHIS = General Hedonic Intensity Scale (−100: 100). C: Group-level sucrose and erythritol across both caloric labels. **** significant difference $p < 0.0001$. D: Individual sucrose and erythritol across both caloric labels.

posteromedial orbital gyri (pmOG), right pOFC, left superior frontal gyrus (SFG), left superior colliculus (SC) in the brainstem, left piriform cortex (Pir), as well as deactivation in the left portion of the spinal trigeminal nucleus (STN) in the medulla. Detailed results are presented in Fig. 5 and Table 1.

Controlling the GLM model for the average Δ-liking ratings collected after each trial had very little impact on the findings mentioned above.

Lastly, there were no associations between the brain responses and Δ-liking ratings for any of the 2nd level primary or secondary contrasts.

The individual ROI-based analyses further confirmed the lack of differences between the labels, sweeteners, or label-by-sweetener interaction. However, the *sucrose vs. water* comparison revealed significant differences in several ROIs across all three distinct groups of preselected brain areas (taste cortex, reward-related regions and hypothalamus). Specifically, in the taste cortex, the right insular cortex, as well as the reward areas, the dorsal striatum bilaterally, VTA/SN, left lateral OFC (lOFC), right medial OFC (mOFC), and right ventral striatum showed activations. Additionally, the hypothalamus, a key homeostatic region, was also activated. Interestingly, the individual ROI-based analyses also highlighted differences for *erythritol vs. water* within the reward-related ROIs, including activations in the dorsal striatum bilaterally, VTA/SN, left lOFC, right ventral striatum, and deactivation of the left mOFC, as well as activation in the hypothalamus (Table 2). Notably, none of the taste cortex regions were differently activated for *erythritol vs. water*.

3.2.3. *Whole-brain multivariate response patterns mediate differences in liking rating*

The whole-brain multivariate mediation (PDM) analysis identified four brain response patterns mediating the differences in liking ratings between *sucrose vs. erythritol*, irrespective of caloric label, as shown in Fig. 6. Path *a* represents the effect of the sweetener *(sucrose vs. erythritol)* on the brain mediator pattern response, which consists of voxels with positive PDM weights (warm colors) indicating the region's activation in response to *sucrose vs. erythritol* and negative PDM weights (cold colors) indicating deactivation. Path *b* represents the association between the brain mediator pattern response and the difference in liking ratings between the two sweeteners, independent of the caloric label.

The first (β=0.1636) and third (β=0.0740) response patterns had positive coefficient values for path *b* ("mediators"), implying that regions with increased or decreased activity in this pattern have a positive association with the differential liking ratings for *sucrose vs. erythritol.* Specifically, this means that regions activated or deactivated in response to the sweeteners are associated with higher or lower liking ratings, respectively, after controlling for the sweetener effects. These patterns included activation of the cerebellum, brainstem (pons, medulla), ventral and dorsal temporal pole (TGv, TGd), anterior part of superior temporal gyrus (STGa), AI, ACC, aMCC, IFG, superior parietal,

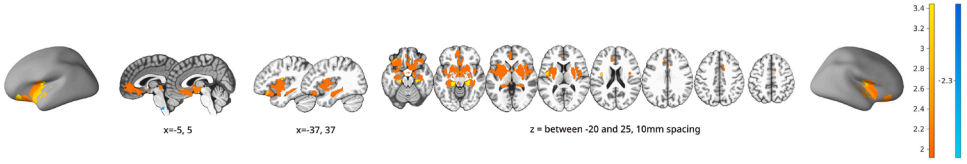

Fig. 5. Results of the parcel-wise GLM analyses within the mask of regions contrasting sucrose with water. Results are thresholded at qFDR < 0.05. Orange colors indicate activations. Blue colors indicate deactivation. Colorbar indicates t-statistics.

Table 1
Results of the parcel-wise GLM analyses within the mask of regions contrasting sucrose with water. Results are thresholded at qFDR < 0.05. X, Y, Z correspond to peak voxel coordinates in MNI space. % covered by label is the percentage of the region covered by the label, atlas regions covered counts the number of the atlas regions covered by at least 25 % by the analysed region, indicating its coverage of multiple atlas regions. When a large cluster covers multiple regions, the volume, coordinates and maxZ values are identical as they refer to the cluster. MaxZ represents the signed maximum Z-score derived from the T-statistic. The label is defined as a reference region with highest number of in-region voxels.

Cluster	Volume	X	Y	Z	maxZ	Atlas label	FDR <0.05	Region	% covered by label	Atlas regions covered
Sucrose *vs.* Water										
1	163,639	−1	2	−9	3.44	Putamen	0.039	Putamen	10	52
1						Nucleus Accumbens (NAc)	0.028	Ventral striatum		
1						Sublenticular Extended Amygdala (SLEA)	0.007	Amygdala		
1						Amygdala Centromedial (CM)	0.007	Amygdala		
1						Amygdala Superficial (SF)	0.018	Amygdala		
1						Globus Pallidus external (Gpe)	0.004	Globus pallidus (basal ganglia)		
1						Globus Pallidus internal (Gpi)	0.014	Globus pallidus (basal ganglia)		
1						Ventral Pallidum (VeP)	0.011	Ventral pallidum (basal ganglia)		
1						Hypothalams	0.003	Hypothalamus		
1						Middle Insula (MI) left	0.046	Insula		
1						Middle Insula (MI) right	0.062	Insula		
1						Pirifrom cortex	0.053	Insula		
1						Posterior Insula (PI) 2 left	0.015	Insula		
1						Posterior Insula (PI) 2 right	0.029	Insula		
1						Frontal Operculum (FO) 1 left	0.032	FO		
1						Frontal Operculum (FO) 1 right	0.030	FO		
1						Frontal Operculum (FO) 2 right	0.002	FO		
1						Frontal Operculum (FO) 2 left	0.006	FO		
1						Frontal Operculum (FO) 3 left	0.043	FO		
1						Frontal Operculum (FO) 3 right	0.041	FO		
1						Area 25 left	0.015	Subgenual anterior cingulate cortex (sgACC)		
1						Area 25 right	0.045	Subgenual anterior cingulate cortex (sgACC)		
1						Area s32 right	0.055	Subcallosal cingulate cortex (SCC)		
1						Area anterior 24 (a24) left	0.038	Subcallosal cingulate cortex (SCC)		
1						Area anterior 32 prime (a32pr) right	0.034	Anterior midcingulate cortex (aMCC)		
1						Superior Colliculus (SC) left	0.045	Midbrain		
1						CA1 Hippocampus	0.021	Hippocampus		
1						CA2 Hippocampus	0.059	Hippocampus		
1						CA3 Hippocampus	0.014	Hippocampus		
1						DG Hippocampus	0.016	Hippocampus		
1						Subiculum	0.002	Hippocampus		
1						Area 47 s (47 s) left	0.038	Inferior Frontal Gyrus (IFG)		
1						Posteromedial Orbital Gyri (OG) right	0.038	Posterior OFC (pOFC)		
1						Area 47 m (47 m) right	0.028	Inferior Frontal Gyrus (IFG)		
1						Area 10r left	0.016	Superior Frontal Gyrus (SFG)		
1						Area 10pp left	0.039	Superior Frontal Gyrus (SFG)		
1						Area 13l left	0.007	Posteromedial Orbital Gyri (pmOG)		
1						Area 13l right	0.027	Posteromedial Orbital Gyri (pmOG)		
1						Subthalamic nuclei (STN)	0.014	Thalamus		
2	6132	−9	22	32	2.23	Area posterior 32 prime (p32pr) left	0.066	Anterior Midcingulate cortex (aMCC)	21	2
3	3664	10	14	40	2.33	Area posterior 32 prime (p32pr) right	0.027	Anterior Midcingulate cortex (aMCC)	40	1
4	860	−3	−37	−53	−2.30	Spinal Trigeminal Nucleus (SN) left	0.029	Medulla	30	2

somatomotor, and visual cortices, as well deactivations in the cerebellum, thalamus, SFG, aMCC, and somatomotor cortex. The second (β=−0.1576) and fourth (β=−0.0522) patterns were negative ("suppressors"), implying negative associations of the activated and deactivated regions with the differences in liking ratings, after controlling for the sweetener effects. Activated regions included the cerebellum, midbrain, SFG, thalamus, TGv, aMCC, IFG, superior parietal, perirhinal, retrosplenial, somatomotor, and visual cortices, whereas deactivated regions included the cerebellum, medulla, amygdala, thalamus, hypothalamus, hippocampus, TGd, perirhinal, somatomotor, and visual cortices. The montages of all four brain response patterns are shown in *Supplementary Fig. 3*.

3.2.4. Whole-brain multivariate brain response patterns predict sweetness liking ratings across sweeteners

Lastly, we aimed to test whether BOLD brain responses across both sweeteners and both labels could predict individual sweetness liking ratings. Cross-validated LASSO-PCR results are described in the Supplement.

3.3. Additional analyses

3.3.1. Bayesian GLM

Due to the lack of significant findings for any of our primary contrasts of interest, we complemented our final parcel-wise frequentist

Table 2
Results of the individual ROI-based analyses across key taste, reward and homeostatic regions. The contrasts represent each sweetener *vs.* water. There were no significant differences between sucrose *vs.* erythritol. The results are thresholded at qFDR < 0.05, with significant values in bold.

Contrast	Groups of regions	Mean value	Standard Error	T-value	FDR	Cohen's d
Sucrose *vs.* Erythritol						
	Homeostatic: hypothalamus	−0.0176	0.0478	−0.3685	0.8213	−0.0673
	Reward:lateral OFC left	0.0273	0.0504	0.5420	0.8213	0.0990
	Reward:lateral OFC right	0.1197	0.0459	2.6086	0.1797	0.4763
	Reward: medial OFC left	0.0984	0.0477	2.0622	0.3047	0.3765
	Reward: medial OFC right	0.0167	0.0355	0.4698	0.8213	0.0858
	Reward: putamen and caudate left	−0.0013	0.0369	−0.0344	0.9728	−0.0063
	Reward: putamen and caudate right	0.0190	0.0292	0.6482	0.8213	0.1184
	Reward: SN and VTA	0.0076	0.0386	0.1962	0.8777	0.0358
	Reward: ventral striatum left	−0.0448	0.0901	−0.4972	0.8213	−0.0908
	Reward: ventral striatum right	0.0439	0.0458	0.9589	0.8213	0.1751
	Taste: insula left	−0.0027	0.0487	−0.0545	0.9569	−0.0100
	Taste: insula right	0.0471	0.0431	1.0950	0.8213	0.1999
	Taste: operculum left	0.0255	0.0610	0.4175	0.8213	0.0762
	Taste: operculum right	0.0361	0.0492	0.7340	0.8213	0.1340
Sucrose *vs.* Water						
	Homeostatic: hypothalamus	0.1033	0.0485	2.1302	**0.0418**	0.3889
	Reward:lateral OFC left	0.1441	0.0423	3.4098	**0.0034**	0.6225
	Reward:lateral OFC right	0.0272	0.0240	1.1344	0.2659	0.2071
	Reward: medial OFC left	−0.0160	0.0279	−0.5708	0.5725	−0.1042
	Reward: medial OFC right	0.0507	0.0180	2.8112	**0.0088**	0.5133
	Reward: putamen and caudate left	0.0631	0.0238	2.6546	**0.0128**	0.4847
	Reward: putamen and caudate right	0.0671	0.0222	3.0185	**0.0053**	0.5511
	Reward: SN and VTA	0.0695	0.0334	2.0798	**0.0465**	0.3797
	Reward: ventral striatum left	0.0319	0.0405	0.7865	0.4379	0.1436
	Reward: ventral striatum right	0.1142	0.0348	3.2778	**0.0034**	0.5985
	Taste: insula left	0.0649	0.0318	2.0400	0.0505	0.3725
	Taste: insula right	0.0815	0.0360	2.2611	**0.0314**	0.4128
	Taste: operculum left	0.0814	0.0457	1.7822	0.0852	0.3254
	Taste: operculum right	0.0856	0.0429	1.9940	0.0556	0.3641
Erythritol *vs.* Water						
	Homeostatic: hypothalamus	0.1121	0.0464	2.4135	**0.0223**	0.4406
	Reward:lateral OFC left	0.1304	0.0411	3.1745	**0.0035**	0.5796
	Reward:lateral OFC right	−0.0326	0.0340	−0.95982	0.3451	−0.1752
	Reward: medial OFC left	−0.0652	0.0316	−2.0644	**0.0480**	−0.3769
	Reward: medial OFC right	0.0424	0.0215	1.9722	0.0582	0.3601
	Reward: putamen and caudate left	0.0637	0.0232	2.7449	**0.0103**	0.5012
	Reward: putamen and caudate right	0.0577	0.0235	2.4523	**0.0205**	0.4477
	Reward: SN and VTA	0.0657	0.0320	2.0550	**0.0490**	0.3752
	Reward: ventral striatum left	0.0542	0.0371	1.4617	0.1546	0.2669
	Reward: ventral striatum right	0.0923	0.0287	3.2133	**0.0032**	0.5867
	Taste: insula left	0.0662	0.0350	1.8927	0.0684	0.3456
	Taste: insula right	0.0579	0.0378	1.5309	0.1366	0.2795
	Taste: operculum left	0.0686	0.0493	1.3919	0.1745	0.2541
	Taste: operculum right	0.0676	0.0399	1.6929	0.1012	0.3091

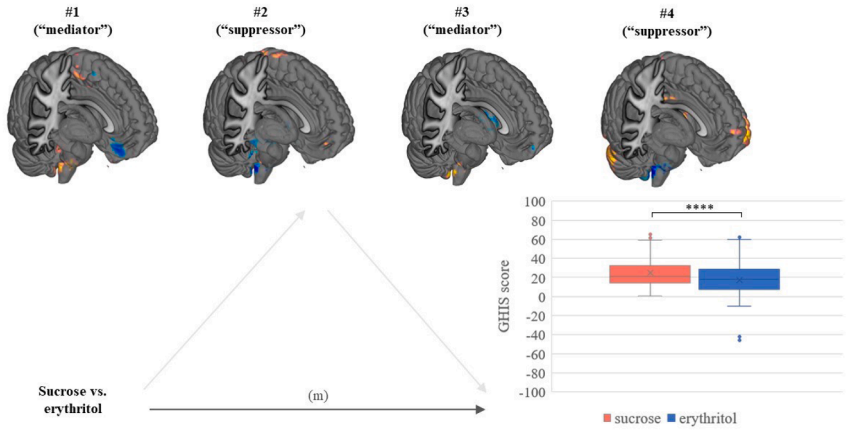

Fig. 6. Results of the whole-brain multivariate mediation (PDM) analyses identifying distinct brain response patterns mediating the differences in liking ratings between sweeteners. Four brain response patterns associated with the difference in liking ratings between sucrose *vs.* erythritol thresholded at qFDR < 0.05.

GLM model with a Bayesian version of the model, to test the relative evidence in favour of the alternative *vs.* the null hypothesis. The IFG was the only region surviving the $0.333 > BF > 10$ thresholding, depicting 'strong' evidence in favour of the alternative hypothesis for both the *high- vs. low-calorie label* (right IFG) and *sucrose vs. erythritol* (left IFG) contrasts. For the *label-by-sweetener* interaction, no region showed strong evidence in favour of the alternative hypothesis. For *erythritol vs. water* the $0.333 > BF > 10$ thresholding showed strong evidence in favour of the alternative hypothesis in the hypothalamus, but not in any other region. For *sucrose vs. water*, strong evidence in favour of the alternative hypothesis was found in the left frontal operculum, left IFG, as well as hypothalamus, and hippocampus, which is mostly in line with our findings of the frequentist GLM. Moreover, at a threshold for 'moderate' evidence $0.333 > BF > 3$, the evidence in the vast majority of regions was in favour of the null hypothesis for the three main contrasts of interest, thereby corroborating the lack of findings in the frequentist analyses. Similarly, a number of regions showed evidence in favour of either the null or alternative hypothesis for the comparisons of both sweeteners with water, in line with the differences found in the frequentist analyses. The detailed results at the $0.333 > BF > 10$ threshold are presented in *Supplementary Table 3*.

3.3.2. Support vector machines discriminate poorly between sweeteners and caloric labels

Cross-validated whole-brain SVM results are detailed in the Supplement.

3.3.3. Responses of the neurobiological signatures for pleasure and craving

For the pleasure signature, no significant differences in pattern expression were found for any of our primary contrasts of interest (main effect of label, main effect of sweetener, interaction of label and sweetener). However, for *sucrose vs. water*, a significant medium-sized positive pleasure signature response were found (dot product 0.03 ±0.01, $t(29)=3.66$, $p = 0.0009$, Cohen's $d = 0.67$). Moreover, *erythritol vs. water* showed a small-sized positive response at trend level (dot product 0.02±0.01, $t(29)=1.95$, $p = 0.06$, Cohen's $d = 0.36$))(*Supplementary Fig. 6*).

For the craving signature, *sucrose vs. erythritol* showed a medium-sized positive response (dot product 1.02±0.41, $t(29)=2.45$, $p = 0.02$, Cohen's $d = 0.44$). This was driven by the pattern specific to drug craving (dot product 0.79±0.38, $t(29)=0.85$, $p = 0.04$, Cohen's $d = 0.38$), rather than food craving, which was not significant (*Supplementary Fig. 7*). For all other primary and secondary contrasts of interest, neither the overall craving nor the drug or food craving signatures were significant.

4. Discussion

This study aimed to assess the impact of food labels manipulating beliefs and expectations about caloric content on subjective and neural responses to the taste of erythritol *versus* sucrose.

For the *first aim*, we observed that oral sips of erythritol elicited lower subjective liking ratings during scanning compared to sucrose, even when individually matched for sweetness intensity. We did not find any differences in liking ratings between *high- vs. low-calorie labels*, nor for the label-by-sweetener interaction. The significant difference in taste pleasantness between erythritol and sucrose is in line with our previous study, where participants received oral sips of erythritol and sucralose solutions matched to the sweetness intensity of 10 % sucrose. In that study, we also reported that erythritol liking ratings were lower than those for sucrose. However, we also showed a significant positive association between higher liking and higher intensity ratings across sweeteners (Budzinska, 2024). In the present study, we confirmed that higher concentrations led to overall higher liking ratings, but erythritol liking ratings remained lower than those for sucrose. This suggests that other characteristics than sweetness intensity, such as for example a chemical (*i.e.* medicinal or artificial) taste (Wee, 2018; Tan, 2019) may make erythritol's taste less pleasant than that of sucrose. The negative findings for the effect of the label and label-by-sweetener interaction on the liking ratings are in line with another fMRI study where participants received small sips of lemonade that was either labelled or mislabelled with high- or low- calorie labels. They also did not find any differences in liking ratings between both caloric labels (van Rijn, 2017). Similarly, Veldhuizen *et al.* who presented a "treat" or "healthy" label upon administration of two low-calorie beverages, did not find any differences in liking ratings between the labels (Veldhuizen, 2013), neither did Crum et al., when serving participants milkshakes with either "indulgent" (high calorie) or "sensible" (low calorie) labels (Crum, 2011). Moreover, several behavioural studies have shown differences only in the expected, but not perceived, pleasantness in response to various nutritional claims and labels on food products and drinks (Rramani, 2023; Oostenbach, 2019).

For our *second aim*, we compared brain responses to oral sips of erythritol and sucrose in combination with a high- and low-calorie label (each sweetener was labelled correctly and mislabelled). Analyses were performed at the voxel- and parcel-level within a mask of predefined taste, reward, and homeostatic areas and complemented by individual ROI-based analysis in seven key ROIs covering the primary taste cortex, reward-processing regions, and hypothalamus. We found no significant differences for any of the above-mentioned contrasts of interest (main effects of sweetener, label, and their two-way interaction) in both the voxel- and parcel-based analyses, including when controlling the GLM models for the average Δ-liking ratings. The individual ROI-based analyses also did not reveal any differences for any of the contrasts. These findings were largely confirmed by Bayesian parcel-wise GLM analyses, as activity in the majority of regions at the moderate evidence threshold $0.333 > BF > 3$ was in favour of the null rather than the alternative hypothesis. However, at the strong evidence threshold $0.333 > BF > 10$, the IFG did show strong evidence in favour of the alternative hypothesis for the main effects of sweetener and label. This depicts a small discrepancy between the frequentist and Bayesian analyses, which might arise from differences in methodology such as handling of uncertainty measures and parameter estimations (Kruschke, 2016). Interestingly, the Bayesian GLM also revealed lateralization of the IFG, as the effect of the sweetener (right IFG) was found on the contralateral side of the effect of the label (left IFG). The IFG is involved in various cognitive functions but has also been implicated in reward processing and decision-making, particularly in evaluating and responding to reward-related stimuli, including tastes (Du, 2020; Dietsch, 2023). The lateralization observed in our Bayesian analyses suggests that the IFG's role might be context-dependent, with the right IFG being more involved in processing the sensory and reward-related aspects of taste and the left IFG being more engaged in cognitive processing related to interpreting and responding to caloric labels. Additionally, the IFG has also been shown to be sensitive to attentional load and the switching of tasks (Hampshire, 2010), which might explain its differential activation in response to the opposing caloric labels and sweeteners. Given this distinct lateralization and absence of a label-by-sweetener interaction effect in the IFG, its responses to sweeteners and labels are likely independent, rather than interactive. The lack of differences in the frequentist analyses between sucrose and erythritol supports our previous findings (Budzinska, 2024). This result is especially noteworthy because we increased the concentration of both sweeteners (erythritol was individually matched to the sweetness intensity of a 16 % sucrose solution in the present study, compared to 10 % in our previous work), which would typically amplify any differences between the sweeteners (Zhang, 2014; Schiffman, 1995). Only a few fMRI studies compared neural responses to oral administration of caloric *vs.* NCS solutions and showed mixed results. For example, Van Rijn *et al.* administered solutions of caloric and non-caloric sweeteners matched to the objective sweetness of 10 % sucrose. Participants consumed a total of 24 mL of each solution in 2 mL sips. They did not find any differences between the

sweeteners in any of their ROIs, which included areas involved in taste, reward, homeostatic, and memory processing (van Rijn, 2015). On the contrary, Smeets et al. found greater activation in the right amygdala and right lateral OFC after oral administration of 2 mL of orangeade containing 10 % sucrose or NCSs objectively matched for sweetness (Smeets, 2011). However, participants in their study consumed a total of 450 mL of the orangeades on the test day (including before the scan), which is significantly more than the volume used in our (36 mL per solution) and other studies. Similarly, Frank et al. observed greater activation in the FO/AI, caudate, SFG, ACC, and ACC in response to the oral taste of 10 % sucrose compared to sucralose (Frank, 2008). In their study, an fMRI block design was used, administering sweeteners 20 times in 1 mL sips, totalling 50 mL per sweetener. Although these amounts are more comparable to ours, their study did not include rinsing between taste stimulations and the block design might have led to potential carry-over and habituation effects, which we aimed to avoid by using an event-related design. To conclude, the rather small volumes in the present study may explain the lack of observed differences between the sweeteners. Therefore, future studies should consider a design that allows for the administration of larger volumes, while considering potential confounding GI side effects of erythritol at higher concentrations (Wölnerhanssen, 2021).

Regarding the lack of differences between the caloric labels, our findings partly align with another study by Van Rijn *et al.* They used high- or low-calorie labels while delivering the same lemonade and did not find differences in any of the a priori regions included in their mask, which consisted of the OFC, ACC, amygdala, caudate, putamen, pallidum, and SN. However, ROI-based analyses in the putamen showed higher activation for the low-calorie label compared to the high-calorie label (van Rijn, 2017). Conversely, another study by Veldhuizen *et al.* used verbal descriptors to modulate brain responses after communicating the delivery of either a "healthy" or a "tasty" labelled drink, which was always low-caloric. They found increased activity in the midbrain and hypothalamus for the "tasty" label compared to the "healthy" label (Veldhuizen, 2013). Additionally, many other studies have demonstrated the power of beliefs in modulating brain responses to food. Despite sharing some similarities, these findings are not entirely consistent across studies. The common denominator between our study and those by Van Rijn et al. and Veldhuizen et al. is the use of health-related labels. In contrast, other studies mostly used descriptors suggesting better taste or higher prices of the presented food stimuli (Plassmann, 2008; Grabenhorst, 2013, 2008). The inconsistency in results from studies testing the effect of health-related labels might stem from variations in participants' education levels, sex, or BMI, which may lead to differences in their awareness and interest in nutrition (Davy, 2006; Lê, 2013; Shepherd, 2007). Van Rijn et al. included only highly educated women, who tend to have more positive attitudes toward healthy eating. Their homogeneous sample might explain the overall negative results for the comparison of high- and low-calorie labels, except for the selective activity in the putamen, positively correlating with the participant's general health interest. In contrast, Veldhuizen et al.'s study included a mixed-gender sample ranging from normal to obese, which may have led to a higher likelihood of observing effects in response to health-related labels. We only included healthy male students with a normal BMI, which may have not only reduced the heterogeneity of our sample but also potentially the modulatory effect of high- *vs.* low-calorie cues. This is supported by many studies showing that brain responses to caloric labels and images in regions related to cognition and reward processing are stronger for women than for men (Killgore, 2010; Cornier, 2010; Uher, 2006). The same applies to individuals with obesity compared to normal-weight (Yunker, 2021), which can even reverse after bariatric surgery (Pursey, 2014; Cornil, 2022). Consequently, our relatively small, male-only homogenous sample represents an important limitation, underscoring the need for future studies with larger and more diverse samples to enhance the generalizability and reproducibility of caloric label effects.

For interpretation purposes, we also compared brain responses to both sweeteners *vs.* water. There were no differences in the voxel-wise analyses, but the parcel-wise GLM analyses did reveal significant differences between sucrose and water, although not between erythritol and water. Specifically, the contrast *sucrose vs. water* showed activations in the amygdala, basal ganglia (putamen, NAc, globus pallidus, and ventral pallidum), hypothalamus, hippocampus, subiculum, bilateral MI, PI, FO, cingulate cortex, IFG, mOG, right pOFC, SFG, left SC, left Pir, as well as deactivation in the left medulla. These regions largely overlap with those found in other studies that compared sucrose with water (Roberts, 2020). In our previous study with a similar design but lower concentrations, *sucrose vs. water* resulted only in ACC deactivation (Budzinska, 2024). The greater number of regions showing differential activation in the current study compared to our previous one, again emphasizes that increasing sucrose intensity amplifies the differences between sucrose and water. Similarly, the individual ROI-based analysis indicated differences across all three groups of ROIs (taste, reward-related, and homeostatic). For *erythritol vs. water*, no differences were found in both the voxel- and parcel-wise GLM analyses. This contradicts our previous study, which found amygdala activation (Budzinska, 2024). A possible explanation for the absence of differences in amygdala activity might be the cognitive modulation by the caloric labels in this study, which possibly shifted the participants' focus from the sensory properties of the sweetener to its expected caloric content, resulting in diminished responses of the amygdala which is sensitive to emotional and reward aspects of taste (O'Doherty, 2001). However, in the current study, the individual ROI-based analyses did show differential activation in reward-related (dorsal striatum bilaterally, VTA/SN, left lOFC, left mOFC, right ventral striatum) and homeostatic (hypothalamus) regions. The additional Bayesian parcel-wise GLM analyses confirmed the findings of the frequentist analysis. At a strong evidence threshold ($0.333 > BF > 10$), responses in the left FO, right IFG, hypothalamus, hippocampus, and globus pallidus differed for *sucrose vs. water*. In contrast, no regions supported the alternative hypothesis for *erythritol vs. water*, which aligns with the frequentist version of the GLM.

For all contrasts, controlling for Δ-liking ratings did not change any of the findings from the model without any covariate, indicating that liking ratings did not impact neural responses to sweeteners nor labels.

Interestingly, despite the lack of significant differences between sucrose and erythritol in the GLM model within our mask of regions, whole-brain multivariate PDM analyses did reveal several distinct brain response patterns mediating the differences in subjective sweetness liking ratings between these sweeteners. Specifically, we found four distinct response patterns mediating the difference in liking ratings between *sucrose vs. erythritol*. Two of these patterns were positively associated, and two negatively associated with the liking ratings for the respective contrast. These findings are in line with our previous study where we also found several multivariate brain response patterns contributing to the differences in subjective liking ratings, despite the lack of differences in brain responses between the sweeteners in mass univariate GLM analysis (Budzinska, 2024). The patterns of brain activity included some of the regions that were part of our mask of regions and that have previously been linked to taste and reward processing, such as the AI, midbrain, ACC, aMCC, IFG, thalamus, SFG, amygdala and hippocampus, as well as homeostasis (*i.e.* hypothalamus, medulla, pons) (Frank, 2008; Roberts, 2020; van Rijn, 2015; Yeung, 2020). Since the PDM analyses included patterns of brain activity across the whole brain, we found some additional regions that contributed to the differences in liking ratings, including cerebellum, temporal polar (TGv, TGd, STGa), perirhinal, superior parietal, retrospenial, somatomotor and visual cortices. These results are largely consistent with those observed in our previous study.

Finally, we also assessed whether neural responses to erythritol and sucrose, depending on the caloric label, elicited differences in the expression of the neurobiological pleasure and craving signature patterns. None of the primary contrasts of interest yielded a significant

pleasure response. However, some of the secondary contrasts, especially the comparison of sucrose and water showed significant positive pleasure responses, further highlighting that tasting sucrose is associated with a pleasurable affective experience. Although the *erythritol vs water* contrast approached significance, it did not elicit a pleasure response as strong as sucrose. Regarding the craving signature, the contrast *sucrose vs. erythritol* showed a medium positive craving response driven by the drug craving patterns, highlighting sucrose's potential to trigger craving- responses more than erythritol. These findings underscore the differential neural processing of caloric *vs*. non-caloric sweeteners and suggest that sucrose is more desirable and may lead to increased substance-seeking behaviour specific to drug use. Future research should investigate the dynamics between the caloric and non-caloric sweeteners and their addictive potential, considering individual variability in sweetener sensitivity and psychological impacts.

Taken together, manipulating cognition about caloric content did not impact subjective liking ratings nor neural responses in reward, homeostatic, and taste ROIs to oral administration of *erythritol vs. sucrose* in healthy, male participants. Moreover, neural responses to erythritol and sucrose did not differ in frequentist or Bayesian GLM analyses, but the significantly lower liking ratings in response to erythritol compared to sucrose were explained by distinct multivariate brain response patterns in whole-brain PDM analyses. Additional approaches described in the supplement (LASSO-PCR and SVM analyses) allowed the detection of the relationships between patterns of brain activity and behavioural outcomes. By considering the simultaneous activity of each voxel across the whole brain (McIntosh, 2013), we showed more nuanced differences between the substances than those identified in univariate GLM analyses. This is in line with previous studies (Chikazoe, 2019; Schoenfeld, 2004) that were unable to identify neural representations corresponding to different taste types (sweet, sour, bitter, salty) in their ROIs (insula, and primary taste cortex respectively) in univariate GLM analyses, and attributed that to either intra or inter-individual variability in liking ratings or brain activity.

This study has some important limitations to consider. First, while our sample size was adequately powered to detect a small interaction effect for the primary 2 × 2 ANOVA, it may have been underpowered to detect smaller effects in individual contrasts or multivoxel analyses. Future studies with larger sample sizes will be important to replicate and extend these findings, particularly for more subtle effects or multivariate approaches. Thus, the present results should be viewed as part of an ongoing investigation into the neural mechanisms underlying the processing of sweeteners, contributing to the broader, evolving literature on this topic. Second, the difference in liking ratings between sucrose and erythritol may also have been a confounding factor, despite controlling for it in our statistical models. Therefore, it would be useful to further explore the relationship between self-reported pleasantness and neural responses to the sweeteners by explicitly assessing neural responses both within and outside the "liking" neurocircuit. Future studies with larger sample sizes may also offer more robust detection of subtle differences in brain activation associated with pleasantness. Third, administering sweeteners as plain, watery solutions may have influenced perceived pleasantness, warranting further research using erythritol in real food matrices. Finally, the small volumes used in this study limited the assessment of the homeostatic effects of these substances.

5. Conclusions

Caloric labels did not affect subjective liking or neural responses to erythritol compared with sucrose. Erythritol elicited lower subjective liking ratings than sucrose, but brain responses in taste, reward, and homeostatic areas did not differ between the sweeteners. These findings confirm existing research that at low (oral) doses, the brain cannot distinguish caloric *vs*. non-caloric sweeteners. We also found differences in neural activity between sucrose *vs*. water and, albeit to a lesser extent, between erythritol *vs*. water. Finally, in multivariate analysis, we identified distinct brain response patterns mediating the difference in liking ratings between sucrose and erythritol. Regarding the craving signature, sucrose *vs*. erythritol showed a medium positive craving response driven by the drug craving patterns, highlighting sucrose's potential to trigger craving responses more than erythritol. These findings underscore the differential neural processing of caloric *vs*. non-caloric sweeteners and suggest that sucrose may be more desirable than erythritol.

CRediT authorship contribution statement

Aleksandra Budzinska: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Laura Byl:** Investigation. **Fabienne Teysseire:** Writing – review & editing, Methodology, Conceptualization. **Emilie Flad:** Writing – review & editing, Methodology, Conceptualization. **Patrick Dupont:** Writing – review & editing, Supervision, Methodology. **Bettina Wölnerhanssen:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Anne Christin Meyer-Gerspach:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Lukas Van Oudenhove:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Nathalie Weltens:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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.

Acknowledgments

This research has been funded by the Research Foundation - Flanders (FWO) [grant number G0D2420 N, 2020].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2025.121061.

Data availability

Data will be made available on request.

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Further reading

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