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Research report

# Associations between brain structure and perceived intensity of sweet and bitter tastes

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ABSTRACT

Functional neuroimaging studies have identified brain regions associated with human taste perception, but only a few have investigated the associations with brain structure. Here, in this exploratory study, we examined the association between the volumes of 82 regions of interest (ROI) and the perceived intensities of sweet (a weighted mean rating of glucose, fructose, aspartame, neohesperidin dihydrochalcone) and bitter (propylthiouracil, quinine, caffeine) substances in a large Australian healthy cohort from the Queensland Twin IMaging (QTIM, n = 559) study and the perceived intensity of quinine in a large U.S. healthy cohort from the Human Connectome Project (HCP, n = 1101). In QTIM, the volumes of 3 cortical (right cuneus gyrus, left transverse temporal gyrus, right inferior temporal gyrus) and one subcortical structure (both left and right caudate) were associated with more than one taste stimulus ($P < 0.05$) and tended to be associated with both sweet and bitter tastes in the same direction, suggesting these ROIs were more broadly tuned for taste sensation. A further 11 ROIs were associated with a specific taste (*sweetness*: 4; *propylthiouracil*: 3; *caffeine*: 2; *quinine*: 2). In HCP, volumes of 5 ROIs were associated with quinine bitterness. The quinine-left entorhinal cortex association was found in both QTIM ($r = -0.12$, $P = 3.7 \times 10^{-3}$) and HCP ($r = -0.06$, $P = 2.0 \times 10^{-2}$). This study provides the first evidence that, even in healthy people, variation in brain structure is associated with taste intensity ratings, and provides new insights into the brain gustatory circuit.

## 1. Introduction

When we eat, food chemicals are detected by taste receptors in the oral cavity and signals are sent via gustatory nerves to brain regions where taste sensation is generated, so we know what we eat and whether we like it or not [1]. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies show that there are areas in the human brain that respond to taste stimulation that are homologous to those found in other primates [2]. However, identification of these taste-responsive brain regions has been inconsistent across studies [3,4], and this may be due to the use of different taste stimuli and tasks performed, as the brain response can be valence-specific [5] or intensity-specific [6], or, more importantly, the small sample size (n < 100). Therefore, additional knowledge is required to complement findings from functional studies and to construct the gustatory pathway in the human brain.

Structural variation in specific brain regions relates to human senses, such as olfaction [7] and vision [8], and recent evidence suggests that volumetric differences also associate with taste. People with eating disorders, e.g. anorexia nervosa, had larger left gyrus rectus grey

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matter [9,10]. There was a positive association between its size and perceived pleasantness of sucrose among both adult patients and healthy controls [9], whereas an inverse association was found among adolescents [10]. Furthermore, structural alterations can modify taste perception, such that increased perceived intensity, especially for bitterness, was found in epilepsy patients with their right anterior temporal lobe removed compared to matched healthy controls, whereas there was no difference in their perception of vision [11]. These findings suggest a new direction for understanding the linkage between brain regions and taste. Here, we conducted an exploratory study to investigate whether there was an association between brain structure and taste perception using two independent population samples, one from Australia (n = 559) and one from the United States (n = 1101).

## 2. Methods and materials

### 2.1. Sample

For the Australian sample, participants were a subset of the Brisbane Adolescent Twin Study (BATS) [12], consisting of 59 complete monozygotic and 107 complete dizygotic twin pairs and 285 unpaired twins or singleton siblings, from 361 families. The sample included 351 females and 208 males and all of them were right-handed and healthy. Participants completed the taste test at age 16.7 ± 2.7 standard deviations (SDs) years, and were MRI scanned approximately 5.0 ± 1.5 SDs years later (mean age at scan = 21.7 ± 3.2 SDs years), as part of the Queensland Twin IMaging (QTIM) study [13]. Prior to scanning, participants were screened for neurological and psychiatric conditions, including loss of consciousness for more than 5 min, and general MRI contraindications. Zygosity of same-sex twin pairs was determined using a commercial kit (AmpFISTR Profiler Plus Amplification Kit, ABI) and later confirmed by genome-wide single nucleotide polymorphism genotyping (Illumina Human610-Quad BeadChip). This study was approved by the Human Research Ethics Committees at the University of Queensland, the QIMR Berghofer Medical Research Institute, and the UnitingCare Health. Written consent was obtained from both the participants and their parents (the latter not required for those 18 years and over).

For the United States sample, we used data from the Human Connectome Project (HCP, S1200 release) [14], which includes 1101 adults (597 females, mean age = 28.8 ± 3.7 SDs years, 825 Caucasians) with taste data on quinine perception and brain MRI images collected at the same time. The sample consisted of 136 monozygotic and 77 dizygotic twin pairs and 675 unpaired twins or siblings. The mean handedness score was 65, indicating a right-hand dominance for participants. Usage of data from HCP for replication and meta-analysis was approved by the University of Queensland Human Research Ethics Committee.

### 2.2. Taste test

In QTIM, the taste test has been described previously [15]. Briefly, participants were instructed to taste five bitter ($6.0 \times 10^{-4}$ M propylthiouracil [PROP], $2.0 \times 10^{-4}$ M sucrose octaacetate, $1.81 \times 10^{-4}$ M quinine, 0.05 M caffeine, and $4.99 \times 10^{-6}$ M denatonium benzoate) and four sweet (0.60 M glucose, 0.30 M fructose, $8.0 \times 10^{-5}$ M neohesperidin dihydrochalcone, and $1.4 \times 10^{-3}$ M aspartame) solutions and to rate their perceived intensities using a general Labelled Magnitude Scale (gLMS). Here we used a general sweet factor score, which is a weighted mean accounting for most of the variance in the perceived intensity of the four sweet tastes (71% for glucose, 77% for fructose, 64% for neoherperidine dihydrochalcone, and 59% for aspartame) [16], and individual ratings for three bitter solutions: PROP, a widely studied bitterness phenotype that approximately half of its variance is due to the genetic variation within the bitter taste receptor gene *TAS2R38* [15]; quinine, a commonly used bitter agent to test perceived bitterness and aversiveness; caffeine, a basic ingredient of the most popular bitter drink, coffee, and can have various impacts on brain [17]. Ratings for sucrose octaacetate and denatonium benzoate were not included here because they were less common taste phenotypes, but their results are provided at the end of the supplementary documents.

In HCP, the NIH toolbox was used for taste test [18]. Participants were instructed to taste one bitter solution ($1.0 \times 10^{-3}$ M quinine, which was 5.5 times more concentrated than that used in the QTIM sample) and rate their perceived intensity ratings on a gLMS.

### 2.3. Brain imaging

For QTIM, structural T1-weighted 3D brain images were acquired using a 4 T Bruker Medspec (Bruker, Germany) whole-body MRI system paired with a transverse electromagnetic (TEM) head coil (TR = 1500 ms, TE = 3.35 ms, TI = 700 ms, 240 mm FOV, 0.9 mm slice thickness, 256 or 240 slices depending on acquisition orientation (86% coronal [256 slices], 14% sagittal [240 slices]) and corrected for intensity inhomogeneity with SPM12 before analysis (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Volumes of the 82 regions of interest (ROIs) were extracted using FreeSurfer (v5.3; http://surfer.nmr.mgh.harvard.edu/) as previously reported [19]. These included 34 gyral-based regions from the Desikan-Killiany atlas [20], which is one of the main cortical parcellations used in studying brain structure, plus 7 subcortical volumes, which have been used in several large studies from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium (enigma.ini.usc.edu), from each hemisphere. We followed the QC procedures of the ENIGMA consortium to check the cortical reconstructions and ROI labelling and excluded incorrectly delineated cortical structures from the analysis. For HCP, details relating to MRI acquisition have been reported [14]. Volumes of the same 82 ROIs were extracted for this study. Descriptive statistics of these brain and taste phenotypes are provided in Supplementary Table 1.

### 2.4. Statistical analysis

Association analyses were performed using a linear mixed model implemented in the R package 'hglm' [21]. For QTIM, prior to analysis taste intensity ratings were regressed by age at taste test, sex, and history of otitis media, which were shown to associate with taste ratings [15]. Brain phenotypes were regressed by age at brain scan, sex, and total brain volume ('BrainSeg' FreeSurfer measure). Taste and brain phenotypes greater or smaller than mean ± 3 SDs were considered as outliers and removed from the analysis (up to 40 outliers; see Supplementary Tables for the number of individuals used in each analysis). Covariates included the fixed effect of the time interval between the taste test and brain scan and the random effect of the family relationship matrix with values of 1, 0.5, and 0 assigned to monozygotic twins, dizygotic twins/siblings, and unrelated individuals. Analyses of PROP were further adjusted for the *TAS2R38* genotype because it accounts for nearly half of the variance in PROP [15,22]. Given that the 4 taste phenotypes are correlated [15] and so are the 82 brain phenotypes [23], we used a matrix spectral decomposition algorithm [24] to estimate the number of independent phenotypes to be 3 taste and 55 brain phenotypes. A conservative Bonferroni-corrected significance threshold was set at $P = 0.05/(3 \times 55) = 3.2 \times 10^{-4}$. For HCP, covariates included the fixed effect of age, sex, and total brain volume ('BrainSeg' FreeSurfer measure) and the random effect of the family relationship matrix. Outliers were excluded using the same criteria. For meta-analysis, we combined results from both samples using an inverse-variance weighted approach using the R package "rmeta" [25].

## 3. Results

While no association reached the conservative corrected

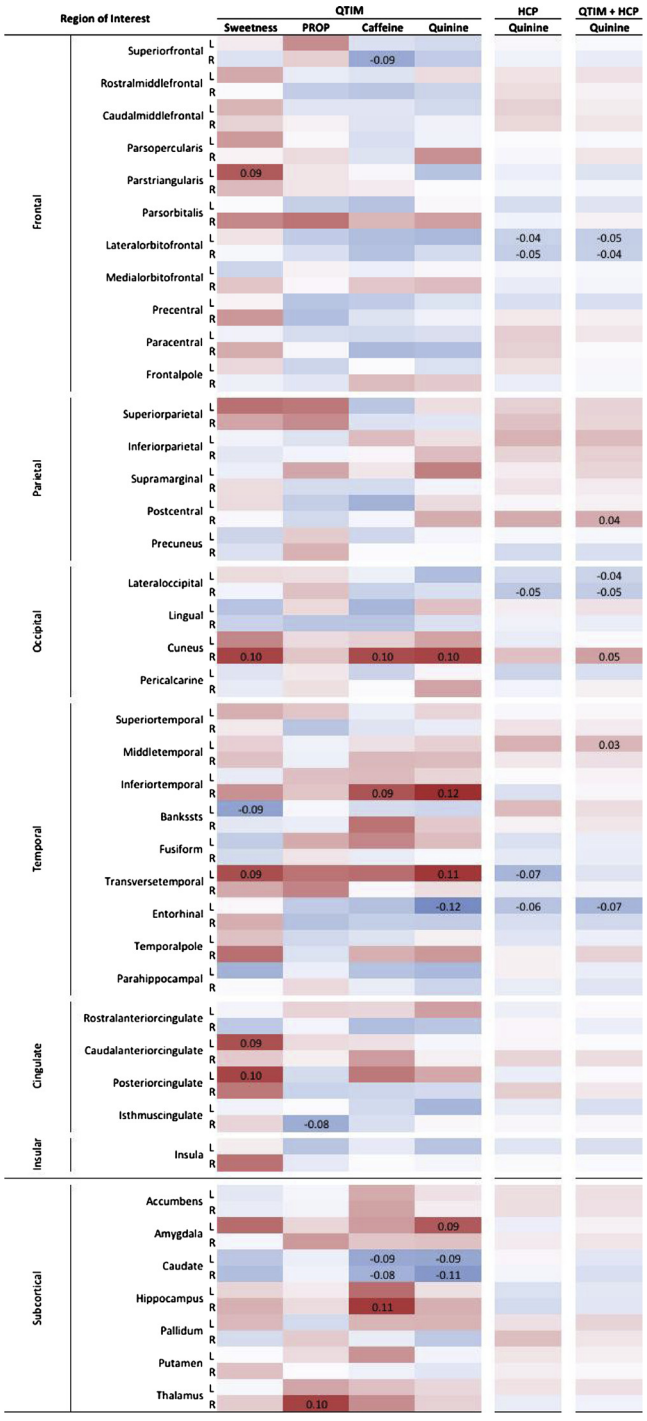


**Fig. 1. Heatmap showing correlations between taste perception and brain structure volumes in QTIM (n = 559) and HCP (n = 1101).** In **QTIM,** *Sweetness* scores were associated with 6 brain regions. For *Bitterness, PROP* scores were associated with 2 regions (increasing to 3 regions after adjusting for the *TAS2R38* genotype; Supplementary Table 4), *Caffeine* and *Quinine* scores with 6 and 7 brain regions respectively. A total of 3 cortical (right cuneus gyrus, left transverse temporal gyrus, right inferior temporal gyrus) and 2 subcortical (left and right caudate) regions were associated with more than one taste phenotype, including both *sweetness* and *bitterness*.
In **HCP**, quinine scores were associated with 5 brain regions. The association with left entorhinal cortex was in the same direction as that found in QTIM, whereas the association with the left transverse temporal gyrus was in the opposite direction. Correlation coefficients with P-value < 0.05 are shown. L and R indicate the volume of left and right hemisphere of the brain respectively.

significance threshold (presented as a heatmap in Fig. 1 [See Supplementary Tables 2–8 for details]), we found several patterns for these associations. ROIs from both hemispheres tended to associate with a taste in the same direction. Using the conventional threshold of $P = 0.05$, in QTIM, the sweetness factor was associated with 6 ROIs and bitter tastes were associated with 4 to 7 ROIs. The volumes of 3 cortical regions (right cuneus gyrus, left transverse temporal gyrus, right inferior temporal gyrus) and 2 subcortical regions (left and right caudate) were associated with more than one taste and tended to be associated with both sweet and bitter tastes. The cortical associations were all positive – larger volumes being associated with increased taste intensity ratings, whereas large left and right caudate volumes were associated with decreased taste intensity ratings. In HCP, the volumes of 5 cortical regions (left and right lateral orbitofrontal cortex, left lateral occipital gyrus, left transverse temporal gyrus, left entorhinal cortex) were associated ($P < 0.05$, all negative) with quinine bitterness.

In QTIM, 11 regions were associated with only one taste ($P < 0.05$). These included 4 cortical regions in the left hemisphere being associated with sweet perception (3 positive associations with pars triangularis, caudal anterior cingulate cortex, and posterior cingulate cortex volumes and a negative association with banks of the superior temporal sulcus), 3 ROIs in the right hemisphere being associated with PROP perception (2 positive associations with pars orbital cortex [only after adjusting for the *TAS2R38* genotype] and thalamus volumes and one negative association with isthmus cingulate cortex), 2 ROIs in the right hemisphere being association with caffeine perception (a positive association with hippocampus volume and a negative association with superior frontal gyrus volume), and 2 ROIs in the left hemisphere being associated with quinine perception (a positive association with amygdala volume and a negative association with entorhinal cortex volume). We note that the *TAS2R38* genotype was not associated with any ROIs ($P > 0.05$), and while the number of ROIs associated with PROP perception increased from 2 to 3 after adjusting for the *TAS2R38* genotype (Supplementary Tables 3 and 4), the overall association pattern did not change significantly.

In HCP, two of the five associations between quinine bitterness and cortical volume were also found in QTIM. The negative association with the left entorhinal cortex volume (QTIM: $r = -0.12$, $P = 3.7 \times 10^{-3}$; HCP: $r = -0.06$, $P = 2.0 \times 10^{-2}$) (Fig. 2) became stronger in the meta-analysis ($r = -0.07$, $P = 5.4 \times 10^{-4}$, Fig. 1). However, the association between the left transverse temporal gyrus volume and quinine bitterness were in opposite directions in QTIM ($r = 0.11$, $P = 6.9 \times 10^{-3}$) and HCP ($r = -0.07$, $P = 3.8 \times 10^{-3}$). For the other 3 associated ROIs in HCP (right lateral occipital gyrus and bilateral orbitofrontal cortex), their corresponding associations with quinine in QTIM tended to be in the same direction, but the meta-analysis results did not reach the Bonferroni-corrected significance threshold (Fig. 1, Supplementary Table 8). In addition, eight ROIs (including left entorhinal cortex) showed suggestive associations ($P < 0.05$) in the meta-analyses and these regions tended to associate with quinine in the same direction in both samples (negative associations: lateral orbitofrontal cortex and lateral occipital cortex in both hemispheres, left entorhinal cortex; positive associations: right postcentral gyrus, left cuneus, left middle temporal gyrus).

## 4. Discussion

In this exploratory study, using the largest available samples (QTIM: n = 559, HCP: n = 1101) we showed that brain morphometry tended to relate with perceived intensity of sweet and bitter tastes. The strongest and most robust association was between the left entorhinal cortex volume and quinine intensity. This negative association was found in both the QTIM and HCP samples, with individuals having larger entorhinal volumes rating the quinine solutions as less intense. The entorhinal cortex is located in the medial temporal lobe [26]. It is believed to make contribution to odour and visual perception. Animal

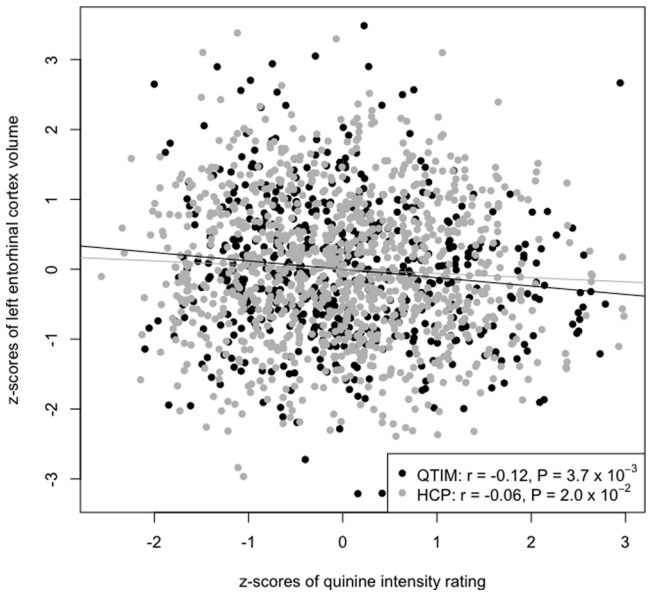


**Fig 2. Scatter plots showing the association between quinine intensity rating and entorhinal cortex volume in QTIM (n = 558) and HCP (n = 1101).** Quinine intensity ratings are adjusted for age and sex and then converted to z-scores. The volumes of left entorhinal cortex are adjusted for age, sex, and total brain volume and then converted to z-scores. Every SD increase in quinine intensity rating is associated with 0.12 and 0.06 SD (i.e. 3% and 2%) decrease in entorhinal cortex volume in QTIM and HCP, respectively. No point is covered by the legend.

studies have demonstrated that lesions in this brain region impair odour [27] and visual [28,29] discrimination, recognition, and identification. Further investigation of this brain region in humans will help interpret our finding specific to taste.

Additionally, in QTIM, we showed that associations between taste perception and brain structure varied across region and taste phenotypes. Five ROIs were associated with more than one taste stimulus and tended to be associated with the perception of both bitterness (quinine and caffeine) and sweetness in the same direction, whereas the association for 11 ROIs (including the left entorhinal cortex) was specific to either sweetness or bitterness, or even just one bitter compound. This suggests that some regions of the brain may be more broadly turned for taste sensation than others. Among the 5 broadly tuned ROIs (right cuneus gyrus, left transverse temporal gyrus, right inferior temporal gyrus, and caudate in each hemisphere), there is some evidence from fMRI [4] and EEG [30] studies that the cuneus and caudate may respond more generally to different taste stimuli (i.e. not only for sweetness and bitterness but also for sourness and saltiness). Similarly, a larger volume of the transverse temporal gyrus, also known as Heschl's gyrus, has been associated with increased perceived intensity of hearing [31]. Here we showed that a larger transverse temporal gyrus, which is the primary auditory cortex, may also be associated with increased perceived intensity of taste. Though we do not have a good explanation for the inverse association found in HCP that a larger transverse temporal gyrus was associated decreased perceived intensity of taste, the discrepancy may be due to two main differences between the studies. In HCP the concentration of the quinine solution was much higher (5.5 times) than that for QTIM and the participants from HCP were approximately 12 years older (QTIM taste test administered at mean age 16.7 ± 2.7 vs HCP: 28.8 ± 3.7 years). Therefore, this finding requires further study and replication.

In contrast to quinine and caffeine, associations for PROP were restricted to three brain regions. We expected the number of associated ROIs to increase after conditioning on the *TAS2R38* genotype. Previously we showed that associations between intensity ratings of PROP and other bitter taste phenotypes became stronger after conditioning on the *TAS2R38* genotype [15]. However, no enhancement was found for the associations between PROP perception and brain volumes. It may be that conditioning on the *TAS2R38* genotype removed nearly half of the variance [15] and the remaining covariance was too weak to be detected in our sample. Alternatively, PROP perception may not covary with brain structure.

With respect to the volume of the primary (anterior insula and frontal operculum) and secondary (orbitofrontal cortex) gustatory cortices, we found no association with the insular cortex in either QTIM or HCP, but there was evidence of an association for regions overlapping with the frontal operculum (i.e. pars orbitalis and sweetness and pars triangularis and PROP after adjusting for *TAS2R38* genotype) in QTIM, and for the lateral orbitofrontal cortex and quinine in HCP. Notably, we previously showed that in QTIM the test-retest reliability for the surface area, which is positively correlated with volume, of insula (r = 0.57 and 0.32 for left and right) was low compared to other ROIs [23]. In a post hoc analysis, we followed a reviewer's suggestion to investigate the association between anterior insula and taste using vertex-wise data (we used the easily accessible data of surface area which is positively correlated with volume). However, none of the associations reached the uncorrected significance threshold ($P > 0.05$ for all) in either QTIM or HCP. In the present study, we did not observe an association between sweetness and left gyrus rectus (medial orbitofrontal cortex), whose volume was previously linked to sucrose pleasantness [9,10]. It is possible that, when tasting a sucrose solution, neural responses in medial orbitofrontal cortex correlate with perceived pleasantness but not perceived intensity [6].

There has been some debate on the lateralization of taste perception and no clear conclusion has been drawn from anatomical and neuroimaging studies [32]. In the present study, associations with the same ROI from each hemisphere tended to be in the same direction, but most of the associations that reached the uncorrected significance threshold were unilateral. This suggests that a specific brain region volume from one hemisphere can be more strongly associated with taste perception than its counterpart in the other hemisphere. This could be because one region of one hemisphere is more variable across people than the corresponding region in the other hemisphere. The valence specific hypothesis, in contrast to the right hemisphere hypothesis, suggests that the left and right hemispheres are specialized for processing positive affect and negative affect respectively [33]. We observed a similar pattern in the present study; associations with sweet taste (n = 4) were all in the left hemisphere, whereas those with bitter taste were more likely to be in the right hemisphere (n for left:right = 3:6). Only two associations, one from each hemisphere, were associated with both sweet and bitter tastes. However, we note that future studies with larger samples are required to validate our findings and to further investigate whether the hemispheric laterality reflects the affective aspect of taste.

We note that the association pattern between taste perception and brain morphometry varies from what has been reported in functional imaging studies. Two of the largest meta-analyses of functional imaging studies [3,4] found no association between taste perception and the entorhinal cortex, and the repeatedly reported gustatory region – insular cortex – was not associated in our work. One explanation for these inconsistencies is that brain regions identified in the present study may be responsible for connecting taste cortices so regardless of tasting status there is no obvious change in the neuronal activity. Alternatively, these results could suggest that other brain phenotypes, e.g. tissue density [34], should be investigated when exploring brain gustatory circuit. In addition, these brain regions may be less variable in volume or less related to individual variation in perceived intensities of tastes.

Our previous twin analyses reported the heritability of taste perception [15] and brain structure [23]. For taste perception, the heritability estimates were 0.36 for sweetness, 0.34 for caffeine, 0.40 for quinine, and 0.73 for PROP. The heritability of the cortical thickness and surface area of these brain regions range from not heritable to 0.65.

As the number of complete twin pairs with both brain and taste phenotypes was limited (QTIM: n = 59 monozygotic and 107 dizygotic twin pairs; HCP: n = 136 monozygotic and 77 dizygotic twin pairs), the genetic correlation between the brain and taste phenotypes was not a focus of the present study, but it can be examined in future studies with a larger sample size.

A limitation of our study is that in the QTIM cohort the taste and brain phenotypes were collected at different times. We included the time interval as a covariate to control for this, and found no significant effects ($P > 0.05$) for any of the associated regions, except for the right inferior temporal gyrus ($P \sim 3.0 \times 10^{-3}$) where a longer time interval led to a larger volume. In addition, in a post hoc analysis where we stratified the sample based on the time interval between collection of the taste and brain phenotypes (i.e. n = 280 with time interval ≤ 5 years and n = 279 with time interval > 5 years) and performed the same regression analyses in the two sub-samples, we showed that though the time interval effect was different across brain regions (Supplementary Fig. 1 and Tables 9–12), the correlations were generally consistent with the associations reported for the full sample. We further showed that the time interval introduced more noise in the association with sweet (r = 0.32 between the correlation coefficients estimated from the two sub-samples; Supplementary Fig. 1) compared to bitter tastes (r = 0.50 for caffeine; r = 0.42 for PROP; r = 0.47 for quinine). This indicates that the perception of both sweet and bitter tastes changes over time from adolescence to early adulthood and the degree of change in sweet taste, previously estimated to be 2–5% lower per year [16], could be greater than that in bitter taste.

Another limitation is the use of anatomical ROIs, which are defined by cortical gyri and sulci, rather than the whole brain vertices. Our preference for the ROI approach over the whole brain approach was mainly due to the limited sample size. Even though we used the largest datasets with both brain and taste phenotypes available (QTIM: n = 559; HCP: n = 1101) our analyses were still under powered. As an exploratory study, the ROI approach could better serve as a starting point, considering that we needed to correct for the significance threshold for testing multiple brain measures. Future studies with larger sample sizes would be more ideal for vertex-wise analyses, which could pinpoint associated brain regions. Further, except for the association with quinine perception, which was collected as part of the HCP, it is not possible to replicate associations for any of the other taste phenotypes because there is no other dataset with both brain imaging and taste phenotypes.

## 5. Conclusion

We show that taste perception is associated with the volumes of specific brain regions among healthy individuals and this provides a new angle on examining the human gustatory cortex in the brain.

## Conflict of interest

The authors claim no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2019.01.046.

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