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Neural processing of basic tastes in healthy young and older adults — an fMRI study

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ABSTRACT

Ageing affects taste perception as shown in psychophysical studies, however, underlying structural and functional mechanisms of these changes are still largely unknown. To investigate the neurobiology of age-related differences associated with processing of basic tastes, we measured brain activation (i.e. fMRI-BOLD activity) during tasting of four increasing concentrations of sweet, sour, salty, and bitter tastes in young (average 23 years of age) and older (average 65 years of age) adults. The current study highlighted age-related differences in taste perception at the different higher order brain areas of the taste pathway. We found that the taste information delivered to the brain in young and older adults was not different, as illustrated by the absence of age effects in NTS and VPM activity. Our results indicate that multisensory integration changes with age; older adults showed less brain activation to integrate both taste and somatosensory information. Furthermore, older adults directed less attention to the taste stimulus; therefore attention had to be reallocated by the older individuals in order to perceive the tastes. In addition, we considered that the observed age-related differences in brain activation between taste concentrations in the amygdala reflect its involvement in processing both concentration and pleasantness of taste. Finally, we state the importance of homeostatic mechanisms in understanding the taste quality specificity in age related differences in taste perception.

Introduction

Adequate dietary intake has been recognized as one of the key factors in maintaining good health, and thereby fostering the quality of life, especially in older adults (i.e. >65 years of age). It is known, however, that food intake changes with advancing age. Whereas food intake is determined by a complex interplay of factors, older adults rank a food's taste as significantly more important than other factors (e.g., biological, economic, physical, and psychosocial factors) (Krondl et al., 1982) compared to young adults. Notwithstanding the relevance of adequate food intake, there is a lack of knowledge on the specific mechanisms underlying age-related changes in taste perception. The aim of the current study was to investigate the neural substrates of taste perception in young and older adults, by manipulating taste quality and taste concentration.

Psychophysiology of age-related changes in taste perception

Several studies have shown that taste perception changes when people age. In these studies two aspects of taste perception have mainly gained attention. First, decreases in threshold taste sensitivity have been observed with increasing age (see for a review: Methven et al., 2012). Age-related changes in taste sensitivity are reflected in both the detection and identification of tastes during threshold taste perception. For example, Mojet et al. (2001) observed that older adults needed a higher taste concentration to detect the presence of either a sweet, sour, salty, or bitter taste using a two-alternative forced choice task (i.e. they had to indicate which of two taste solutions contained the taste compared to a cup with distilled water). In addition to these changes in taste detection, Fukunaga et al. (2005) showed that older adults had more difficulty to correctly identify the taste quality being sweet, sour, salty, or bitter (i.e. taste identification) than young adults. This is in agreement with the study of Landis et al. (2009), in which spoon-shaped filter paper strips were used impregnated with four basic taste qualities in four different concentrations. Landis and colleagues found that with increasing age the overall number of correctly identified strips decreased. The second aspect relevant with respect to taste perception is changes in supra-

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threshold taste discrimination that have been observed with increasing age. It was found that older adults required larger concentration differences in order to experience a difference in stimulus intensity using a three-alternative forced choice test (Kaneda et al., 2000; Kremer et al., 2007).

Although ageing was reported to affect taste perception in general, these age-related changes appear to be taste-quality-specific. With advancing age, taste detection thresholds of bitter stimuli seem to be affected most, followed by sour, salty, and sweet stimuli subsequently (Gilmore and Murphy, 1989; Kaneda et al., 2000; Murphy and Gilmore, 1989). However, Mojet et al. (2001) found a decline in taste detection thresholds only for salty and sour, while they observed no differences between young and older adults for sweet and bitter tastes. Moreover, Weiffenbach et al. (1982) found that taste detection thresholds were affected for salty and bitter tastes, but not for sweet and sour tastes with increasing age. These results confirm that age-related changes on taste perception indeed vary; however, the extent and significance of these taste-quality-specific effects are rather inconsistent across studies.

Mechanisms underlying age-related changes in taste perception

The psychophysical studies mentioned above, showed changes in taste perception as a function of age. With respect to the mechanism underlying these changes, Shin et al. (2012) studied the anatomy of the taste sensory system in mice. It was found that a reduced number of taste cells expressing the sweet taste receptor, was related to reduced sweet taste responsivity in older compared to young mice. However, no decrease in taste bud number in papillae was observed as a function of age in humans (Arvidson, 1979; Mistretta and Baum, 1984). This indicates that changes in anatomy are unlikely to underlie age-related changes in taste perception in humans.

Alternatively, age-related changes in humans might be associated with changes within the neural substrates of the taste sensory system. These changes can either be explained by changes in brain structure, such as reduced grey matter and cortical thickness (Fjell et al., 2006), or by changes in brain function, as reflected in changes in activation patterns in brain responses during taste perception (De Boer et al., 2013; Levine et al., 2000). Although evidence with respect to taste perception is scarce, age-related reductions in parietal activity were observed during the processing of visual information, which were attributed to deficits in sensory processing (Cabeza et al., 2004; Grady et al., 2005). Additionally, reduced activation was observed in older adults in response to tactile stimuli (Brodoehl et al., 2013; Tomasi and Volkow, 2012) in the primary and secondary somatosensory area, areas which were also found to be responsive to taste information.

This study aims to contribute to a better understanding of neural mechanisms underlying age-related changes in taste perception in humans. More specific, in the present study we sought to examine whether the perception of taste indeed differs across young and older adults and whether these differences were dependent on taste quality and/or concentration. In order to do so we used functional magnetic resonance imaging recorded during the perception of basic tastes measured at different brain areas along the taste pathway.

The pathway of taste information processing in the brain

Studies investigating the neural substrates of the taste sensory system elaborate on existing knowledge on taste perception which is mainly based on psychophysical studies. In these studies, taste perception is examined by studying the effect of varying properties of taste stimuli along one or more physical dimensions on an individual's subjective experience as reflected in overt behaviour (e.g., button press or verbal reaction). Whereas these methods do not provide direct information with respect to the underlying mechanisms of age-related changes in taste perception, neuroimaging does enable us to study the neural substrates between a stimulus and its behavioural response.

Information derived from taste cells on the tongue converges via the taste-responsive cranial nerves on the rostral division of the nucleus tractus solitarius (rNTS) of the medulla (Simon et al., 2006). The NTS is involved in coding both taste quality and concentration (Di Lorenzo and Victor, 2003). Ascending pathways subsequently terminate in the ventroposterior medial nucleus of the thalamus (VPM). From there, thalamic afferents project to the primary somatosensory area in the cortex (i.e. the cortical somatotopic sites for the face and oral cavity on the postcentral gyrus) (Boling et al., 2002), and the secondary somatosensory area (i.e. the posterior insula) (Stephani et al., 2011). Small and Prescott (2005) postulated that taste, odour, and associated tactile sensations are integrated in these oral somatosensory areas, to produce a unitary flavour percept. In line with these findings, previous studies showed increased multisensory integration in older compared to young adults for visual–auditory stimuli (DeLoss, Pierce, and Andersen, 2013; Peiffer et al., 2009), as reflected in increased activity in posterior parietal integration areas in older adults (Diaconescu et al., 2013). In addition to the secondary somatosensory area, identified on the posterior insular region, the insula has been subdivided in two other anatomically and functionally meaningful regions (Deen et al., 2011; Nelson et al., 2010). First, the ventral anterior insula, which receives predominantly afferents from the limbic cortex (e.g., amygdala), and is described as the primary taste cortex. This area mediates the processing of taste concentration and taste quality (Grabenhorst et al., 2008; Schoenfeld et al., 2004; Smith-Swintosky et al., 1991; see for meta-analysis Veldhuizen et al., 2011). Moreover it modulates perceived pleasantness by manipulation of expectations and beliefs (Berns et al., 2001; Nitschke et al., 2006; Zald, 1998). A previous study indicated that older adults show lower activation in the ventral anterior insula in response to painful stimuli (Quiton et al., 2007), which was argued to reflect changes in affective processing with advancing age. Second, the dorsal anterior insula receives afferents predominantly from the medio-dorsal nucleus of the thalamus. Activation of the dorsal anterior insula has been associated with attention (Eckert et al., 2009; Touroutoglou et al., 2012). For example, Veldhuizen et al. (2011) showed that the dorsal anterior insula was more activated in response to an unexpected taste as compared to the perception of an expected taste.

Besides the pathway from the rNTS to the insular cortex, two subcortical brain areas were implicated in taste processing; the amygdala and the lateral hypothalamus (LH). Regarding the amygdala, it was found that brain activation increases across increasing taste concentrations (Anderson and Sobel, 2003; Small et al., 2003). Also, bitter stimuli were found to elicit a stronger amygdala response in older compared to young adults (Jacobson et al., 2010). However, in the Jacobson et al. study the young and older adults did not differ in threshold taste sensitivity and the subjective pleasantness they expressed after tasting. Therefore, the authors were unable to ascribe the stronger amygdala response to either taste concentration or taste pleasantness. With regard to the LH, it is known that this structure plays an important role in the regulation of homeostasis, motivation and eating behaviour (Li et al., 2013; Smeets et al., 2005; Tokita et al., 2014). For example, an increased response in the LH was observed in response to salty taste during the salt-deprivation condition together with increased motivation towards salty taste (Tandon et al., 2012). The authors suggested that homeostatic state affects the motivational value of particular taste stimulus as reflected LH activation. Moreover, it was found that ageing is associated with the down-regulation of neurotransmitters in the LH involved in motivation and appetite, which has been associated with a loss of weight at the end of life (Kmiec, 2010; McDonald and Ruhe, 2010). In sum, different brain areas are involved in the processing of taste information. Information about age-related changes in these brain areas along the taste pathway is scarce and a more precise localisation of these effects will reveal more insight in possible mechanisms underlying the effects of age with respect to taste perception.

Material and methods

Participants

A group of young ($n = 41$, 21 men, average 23 years of age, SD = 3, range 18–30 years) and older ($n = 36$, 18 men, average 65 years of age, SD = 4, range 60–72 years) healthy adults, without a history of head injury or other neurological conditions participated in this study. All participants were right handed, non-smokers for at least 3 months, reported no oral or nasal complaints and had normal or corrected to normal vision. To ensure that hormone levels were fairly constant, young female participants were only included if they used hormonal anticonceptives. Participants using medication that might affect taste perception (i.e. with reported side effects like gastrointestinal complaints, dry mouth, nausea, and taste disturbance) were excluded from the study. Participants received monetary compensation for participation.

Ethics statement

The study protocol was approved by the medical ethical committee of the University Medical Center Groningen and all participants gave written informed consent before participation.

Task and stimuli

During scanning participants performed four task blocks of approximately 15 min each. Each block consisted of tasting three of the four taste qualities, delivered sequentially in five ascending concentrations (i.e. 0 (equals a rinse), 12.5, 25, 50 and 100% of the maximum concentration stock solutions). A fixed sequence from a low to high concentration results in lower carry over effects than the delivery of random or descending concentrations. Furthermore, a similar concentration sequence was used in all participants in order to reduce the variability of carry over effects across participants. Over four blocks tastes were administered three times in a balanced order. The order was counterbalanced across participants. Task blocks were alternated with rest periods of approximately 2 min. In order to minimize carry over effects that might arise between 1) taste qualities (e.g. effect of pleasant taste followed by an aversive taste and vice versa) and 2) taste concentrations (e.g. effect of intense taste followed by a weak taste) we used the current selected block design instead of an event-related design.

Participants were visually cued for solution delivery with a white asterisk (2 s) followed by the text "taste" for a taste and a blue circle (5.8 s) followed by the text "rinse" for a rinse. Orally delivered taste qualities were sweet (100%: 560 mM sucrose), salty (100%: 180 mM NaCl), sour (100%: 10 mM citric acid) and bitter (100%: 1 mM quinine HCl) (Bender et al., 2009; Jabbi et al., 2007; Rolls, 2011). For the rinsing and dilution of the tastes, demineralized water was used. Stimuli were all delivered in volumes of 2 ml over 3 s, using an in-house designed MRI-compatible taste system. This system consists of 30 syringes, operated by the experimenter following audio cues delivered via headphones. Task instructions were presented on a computer monitor using E-prime (Psychology Software Tools Inc., Pittsburgh), in white on a black background (Fig. 1).

After tasting and swallowing (3.5 s), participants rated the pleasantness of the taste stimulus on a horizontal 7-point Likert scale (ranging from 1 "very unpleasant" to 7 "very pleasant"). Rating was done using a button box, which was held in the right hand. Subsequently, a rinse was delivered (4 s) and swallowed (3.8 s). Thereafter, a baseline-interval followed, wherein a red cross was displayed on the screen. The baseline-interval lasted for 6 s between different taste concentrations and 15 s between different taste qualities. In total, the protocol lasted for approximately 90 min, during which 264 ml of liquid was administered.

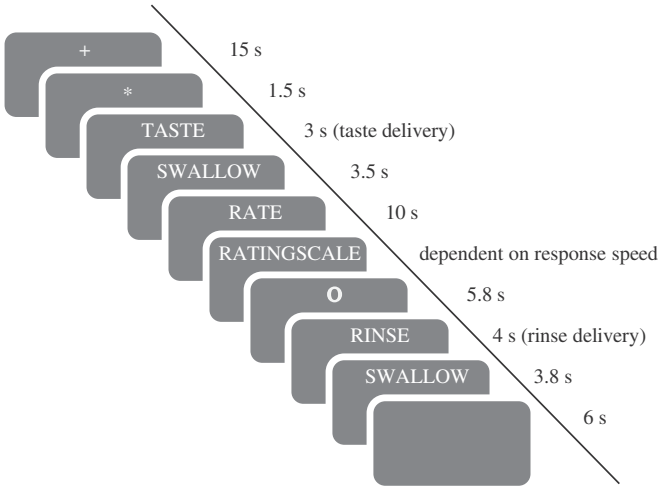

Fig. 1. Taste task. Sequence of taste delivery, rating and rinsing.

Procedure

Participants first participated in a one-hour screening session scheduled between 9.00 and 12.00 a.m.. During this session inclusion criteria were checked, saliva samples were collected (results reported elsewhere), screening for hypogeusia was performed, and participants were familiarized with the experimental procedure. A scanning session during which participants performed the tasting task took place within 7 days from the screening session. Participants were instructed not to eat or drink during 2 hrs prior to the scanning session.

Hypogeusia test

Screening for hypogeusia was conducted using spoon-shaped filter paper strips, which were impregnated with four basic taste qualities in four different concentrations (Landis et al., 2009). Two neutral taste strips were included with no taste concentration impregnated. After the mouth was rinsed with water, participants were asked to place a strip on the middle anterior third of the tongue. Taste qualities were applied in a randomized fashion at each of the four concentrations and in an ascending (i.e. low to high) concentration order. Participants had to identify the taste from a list of five descriptors, i.e. sweet, sour, salty, bitter, or neutral (multiple alternative, forced choice). The whole testing procedure typically required approximately 10 min. The number of correctly reported taste qualities corresponded to an overall 'taste score' ranging between 0 and 18.

Image acquisition

Functional MRI scans were obtained with a 3 T MR scanner (Philips Intera, Best, the Netherlands) equipped with a 32-channel head coil. Functional partial brain images were acquired in coronal orientation covering 81 mm of the cortex capturing the brainstem and insula. Partial brain scans were chosen to optimize coverage of brainstem, thalamus, insula and amygdala. Other areas that previously have been studied in relation to taste processing such as the orbitofrontal cortex (OFC), were not (totally) included in data collection (Fig. 2). The Principles of Echo-Shifting with a Train of Observations (PRESTO: (Van Gelderen et al., 2012)) sequence was used to allow rapid switching of the imaging gradients. The following pulse sequence parameters were used: field of view (FOV) 230 × 230 × 81 mm (rl, ap, fh); voxel size 3.03 × 3.59 × 3 mm; scanning matrix 76 × 64 × 27; repetition time (TR) = 20 ms; echo time (TE) = 30 ms; flip angle 7°; SENSE factors: 2.1, 1.9 (rl, ap); and 27 slices, scan time per volume 0.852 s. In addition,

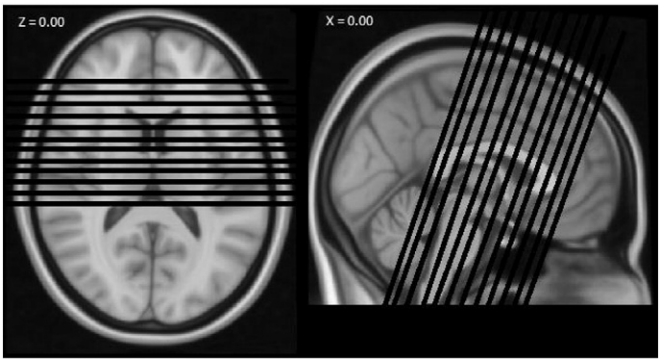

Fig. 2. Image acquisition. A transversal (left) and sagittal (right) view of the brain areas covered in image acquisition. Actual scanning contained 27 slices.

5 full brain PRESTO images were acquired with equal orientation to the partial brain PRESTO images: FOV 230 × 230 × 234 mm; 78 slices; scan time per volume 2.3 s. Furthermore, a T1-weighted 3D fast field echo (FFE) whole brain image was obtained in transverse slice orientation after the first two experimental blocks and the full brain PRESTO images: FOV 256 × 232 × 170 mm (rl, ap, fh); voxel size 1 mm isotropic; TR = 9 ms; TE = 3.5 ms; flip angle 8°; SENSE factors: 2.5, 1 (ap, fh); 170 slices, scan duration = 246.3 s.

Pre-processing and first level analysis of functional images

Pre-processing and first-level analysis of the functional images were performed using the Statistical Parametric Mapping software Version 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2011b (The MathWorks, Natick, MA). During pre-processing, functional images were corrected for motion artefacts (realignment), coregistered to the third full brain PRESTO image as an intermediate step, and subsequently coregistered to the T1 anatomy image. For normalization, Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) was used to create a study specific anatomical template (young and older adults together). The coregistered functional images were normalized to this study specific template optimizing the inter-participant alignment (Ashburner, 2007). Finally, the images were normalized to the Montreal Neurological Institute (MNI) standard template and smoothed with a 6 mm full-width half-maximum (FWHM) Gaussian kernel.

For the first-level statistical analysis, the conditions 'Tasting', 'Swallowing', 'Rate' (i.e. 10 s between swallowing and the actual rating scale) and 'Ratingscale' were entered as separate regressors for each taste stimulus. Thus every condition was modelled 48 times (4 taste qualities × 4 taste concentrations × 3 repetitions). All rinsing conditions (i.e. 'Tasting', 'Swallow', 'Rate', and 'Ratingscale' of the 0% taste concentration and 'Rinse' and 'Swallow' during rinsing) were stacked in a single regressor. Additionally, two regressors (of no interest) were assigned to 'Taste comes' (white asterisk) and 'Rinse comes' (blue circle), respectively, to explain remaining variance to be removed from baseline. The realignment parameters and the first derivatives thereof were entered as covariates to correct for the effects related to head motion (Friston et al., 1996). A high-pass filter with a cut-off of 128 s was applied to remove confounds created by slow signal drifts with a period exceeding this threshold. The task-related regressors were convoluted with the canonical hemodynamic response function (HRF) in order to estimate the amplitude of the brain response (i.e. beta estimates) to the corresponding conditions.

Missing volumes in image acquisition

For technical reasons, several PRESTO images were missing at random time intervals (on average 0.05% of the whole dataset) for 10 participants. To minimize the effect of missing volumes, 1) these volumes were replaced with the first PRESTO volume of the task block, and 2) a separate regressor for each missing volume was added during the first-level statistical analysis.

Group level analyses of behavioural data

The subjective liking ratings obtained during scanning were analysed using linear mixed-effects modelling (LME) using the *lme4* package (Bates et al., 2014) in the open source statistical language R (R Core Team, 2012). The liking rating were compared between *age groups* (two levels: young and old), *taste concentrations* (continuous from 12.5, 25, 50, to 100%) and *taste qualities* (four levels: sweet, sour, salty, and bitter) (fixed effects), while taking into account intra-individual variability by adding *subject* as a random effect. In addition, the three administrations of the same taste concentration were used to calculate a random slope effect, allowing each subject's taste administration to deviate from the overall intercept and slope constituted by the fixed effects.

The taste scores obtained in the hypogeusia test were counted for each taste that was administered (i.e. sweet, sour, salty, bitter, and neutral) and analysed with generalized linear mixed-effects modelling (GLMM) using the *lme4* package. In this model, the taste scores were assumed to be a Poisson function of the predictors *age group* (two levels: young and old) and *taste quality* (four levels: sweet, sour, salty, and bitter).

Model comparisons for both the subjective liking ratings and taste scores were based on likelihood ratio tests using the χ^2 statistic provided in the *lme4* package. We will report both beta estimates and the corresponding p-values for the optimal models.

Group level analysis of functional images

Group-level analysis on fMRI data was performed using the LME as implemented in AFNI (see for details of *3dLME* Chen et al. (2013)). By applying linear mixed effect modelling, we were able to control for intra-individual variability resulting from the repeated taste administrations. Each taste administration was modelled separately in the current voxel-by-voxel group analysis.

At the group level, the amplitudes of the HRF during tasting (i.e. beta estimates of the 3 s tasting interval) resulting from the first-level analyses were modelled voxel-wise in the LME framework. Model estimation within a mask was applied using the grey matter tissue probability map obtained from DARTEL (threshold: $p > .3$). We used four fixed factors: one between-subjects factor: Age group (two levels: young and older adults), and two within-subject factors: Taste quality (four levels: sweet, sour, salty, and bitter) and Taste concentration (four levels: 12.5, 25, 50, and 100%). Note that the current analysis extended conventional group-level analysis like the general linear model (GLM), by enabling interaction effects between age groups, taste qualities and taste concentrations in a single model. The variable Repetition (three levels: three administrations of the same taste concentration) was inserted as a random slope effect, allowing each subject's taste administration to deviate from the overall intercept and slope constituted by the fixed effects. The *F*-maps and *t*-maps were thresholded using $p_{uncorrected} < 0.05$ with an extent of 20 voxels, to identify grey matter regions showing main- and interaction effects. Because of high computational demands that are required for running this model, no model comparisons could be performed. We identified the effects of age on the pattern of the beta estimates over increasing taste concentrations, and whether these effects are taste-quality-specific. For reasons of clarity, we present the findings from activity in task-related brain regions in the order of the gustatory pathway involved in basic taste processing (i.e. from the nucleus solitary tract to the insular cortex and overlying operculum).

Results

Hypogeusia taste scores

Young (average = 12, SD = 2) and older adults (average = 12, SD = 2) showed no significant differences on the taste score for sweet ($beta_{sweet:young-old} = 0.03$, n.s.), sour ($beta_{sour:young-old} = -0.10$, n.s.), salty ($beta_{salty:young-old} = -0.26$, n.s.), and bitter ($beta_{bitter:young-old} = 0.00$, n.s.) tastes.

Subjective liking ratings

Participants liked the sweet taste most (mean $_{sweet} = 5.00$, $beta_{sweet-salty} = 2.41$, $p < 0.001$), followed by sour (mean $_{sour} = 3.42$) and salty (mean $_{salty} = 2.93$, $beta_{sour-salty} = 0.12$, n.s.). Bitter was most disliked (mean $_{bitter} = 1.55$, $beta_{salty-bitter} = 1.48$, $p < 0.001$). In addition, the liking ratings decreased with increasing taste concentrations for bitter taste qualities ($beta_{bitter:concentration} = -0.12$, $p = 0.008$), while the liking ratings of sweet tastes showed an inverted U-shape with increasing concentrations ($beta_{sweet:concentration} = 0.07$, $p = 0.015$). The liking ratings for sour ($beta_{sour:concentration} = -0.01$, n.s.) and salty ($beta_{salty:concentration} = -0.07$, n.s.) tastes did not change across concentrations.

In general the older adults reported higher liking ratings compared to the young participants, however, post-hoc tests showed that this was only observed for sweet ($beta_{sweet:old-young} = 0.34$, $p = 0.039$) and salty ($beta_{salty:old-young} = 0.61$, $p < 0.001$) tastes. There were no significant differences observed between young and older adults for bitter ($beta_{bitter:old-young} = 0.13$, n.s.), while older adults actually reported lower liking ratings for sour tastes ($beta_{sour:old-young} = -0.32$, $p = 0.048$). No interactions were found between age, taste quality and taste concentration (i.e. extending the previous model with interaction terms did not result in a significant improvement for estimating the liking ratings ($\chi^2 = 0.00$, n.s.)).

fMRI data

We present the findings for brain activations in task-related brain regions, in the flow of information in the taste pathway that is from the nucleus solitary tract to the insular cortex and overlying operculum. For each brain regions, the effects of taste concentration are reported first, followed by the effects of taste quality.

Brain overlays of regions representing significant t- and F-test results are presented in the figures. The F-tests are further displayed in bar graphs of the mean beta estimate of all voxels within a significant region (i.e. mean beta estimates across three administrations of the same taste quality (e.g., sweet) and taste concentration (e.g., 100%)) for young (blue) and older (red) participants separately. The results of the linear mixed effect modelling, including F-values and t-values, and anatomical location of significant clusters of activation are reported in Table 1.

Nucleus solitary tract

Group analysis showed that activation levels did not differ between age groups, taste qualities and taste concentrations in this brain area. We neither observed significant interactions between these factors. To ensure the presence of fMRI signal in the rNTS (i.e. the input of the linear mixed model in this area), we extracted mean beta estimates of a sphere with a radius of 3 voxels around the anatomy based MNI coordinates [(−)4.00 −43.00 −45.00] for the left and right NST, respectively. By visual inspection we found that activation patterns in the rNST were indeed modulated by tasting as compared to baseline, which supports the reliability of our findings.

Ascending pathways from the NST–ventral posteromedial (VPM) nucleus of the thalamus

Task related brain activation was found in all taste conditions in both age groups in this brain area. However, no differences were found between young and older participants, and between different taste qualities and taste concentrations.

Ascending pathways from the thalamus–primary somatosensory area

We found enhanced activation in young compared to older participants in the primary somatosensory area. This pattern of results was scattered across the postcentral gyrus. In addition, we observed differences in activity between young and older adults at different taste concentrations on the postcentral gyrus; an area reflecting the homuncular area of the representation of the head and neck. We found the most pronounced ageing effects in the 100% taste concentration condition compared to the lower taste concentrations (Fig. 3). Taste quality did not modulate activity in primary somatosensory area, and no interaction effect was observed in the brain response between age and taste quality.

Reciprocal pathways from the pulvinar nucleus of the thalamus to the association cortex

No differences in brain activation were observed between different taste concentrations, neither did age interact with taste concentration in the pulvinar nucleus of the thalamus. We did observe higher activity in young adults in this area, which was more pronounced for sour taste (Fig. 4), as reflected in the age by taste quality interaction.

Table 1
Regions of significant t- and F-tests: effects within the taste pathway.

Effect and region	Hem.	Peak voxel MNI coordinates			Max. int.	Significance level
		x	y	z		
Age: young–old (# voxels: k > 20)						
Medio-dorsal nucl. (thalamus)	L/R	2.00	−14.00	11.00	t (72) = 8.73	PFWE < 0.05
Taste quality (# voxels: k > 20)						
No effects observed						
Taste concentration (# voxels: k > 20)						
Lateral hypothalamus	L/R	0.00	−4.50	−16.00	F (3.3448) = 3.84	Punc. < 0.05
Age × taste quality (# voxels: k > 20)						
Pulvinar nucl. (thalamus)	R	16.00	−30.00	4.00	F (3.3448) = 5.50	Punc. < 0.05
Lateral hypothalamus	L/R	0.00	−12.00	−8.00	F (3.3448) = 3.03	Punc. < 0.05
Posterior insula	L	−40.00	−36.00	18.00	F (3.3448) = 2.71	Punc. < 0.05
Ventral anterior insula	R	44.00	2.00	−14.00	F (3.3448) = 3.36	Punc. < 0.05
Age × taste concentration (# voxels: k > 20)						
Amygdala	R	16.00	2.00	−20.00	F (3.3448) = 3.12	Punc. < 0.05
Amygdala	L	−28.00	−2.50	−28.00	F (3.3448) = 2.45	Punc. < 0.05
Postcentral gyrus	L	−52.00	−30.00	32.00	F (3.3448) = 4.69	Punc. < 0.05
Posterior insula	L	−34.00	−30.00	14.00	F (3.3448) = 2.70	Punc. < 0.05
Dorsal anterior insula	L	−37.00	26.50	−2.00	F (3.3448) = 2.83	Punc. < 0.05

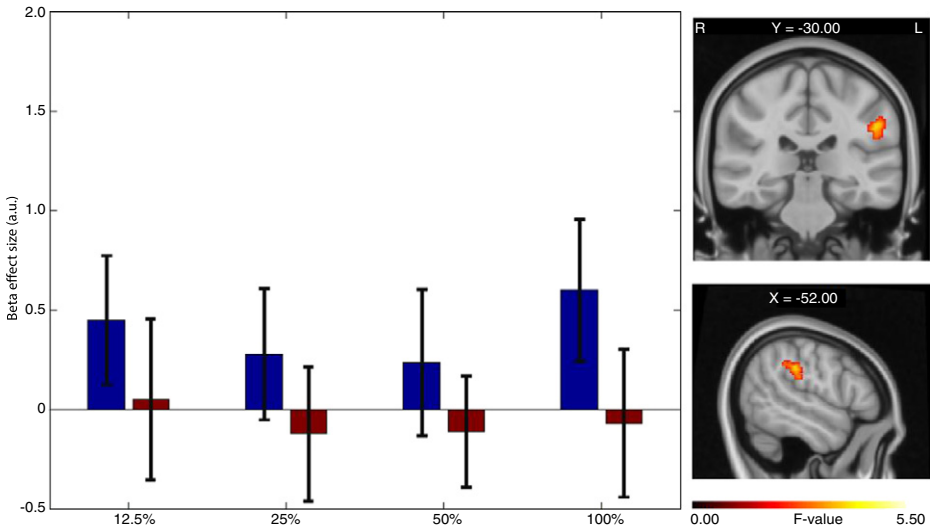

Fig. 3. Primary somatosensory cortex. Bar graphs representing taste concentration effects in young (blue) and older (red) participants.

Ascending pathways from the thalamus–insular cortex

Posterior insular cortex. The brain response in the posterior insular cortex was higher in young compared to older participants, especially in response to the 100% taste concentration (Fig. 5a). Furthermore, age was found to interact with taste quality (Fig. 5b). Remarkable, older participants showed increased brain activity as compared to baseline levels only in the sour condition, while such effects were nearly absent in the other conditions. In young participants, the most pronounced response was shown in response to sour, followed by sweet, salty, and bitter tastes.

Ventral anterior insular cortex. Taste concentration did not modulate activity in the ventral anterior insular cortex; neither did we observe differences in brain activation between age groups dependent on taste concentration in this brain area. We did observe an interaction between age and taste quality, reflecting a smaller brain response in young participants compared to the older participants in response to salty and sour tastes in this brain area. No differences were found between young and older participants in response to sweet and bitter tastes in this area (Fig. 6).

Dorsal anterior insular cortex. We observed an interaction between age and taste concentration in the dorsal anterior insula, indicating that older participants showed more activation than the young adults did in the 12.5% taste concentration condition. This difference was less pronounced or even absent in the higher taste concentration conditions (Fig. 7). Taste quality did not modulate activity in this brain area; neither did age interact with taste quality.

Reciprocal pathways from anterior insular cortex to the amygdala

Activation patterns in the amygdala differed across age groups. Moreover, these effects of age were modulated by taste concentration, as reflected in age by taste concentration interaction (Fig. 8). In the right amygdala, differential activation between young and older participants was mainly observed in the 12.5, 25, and 100% concentration conditions. Visual inspection of Fig. 8 shows a decrease in response in the young participants with increasing taste concentrations, whereas the pattern of activity in older participants was more variable across the different concentrations. To test these effects, we performed an additional linear mixed effect model analysis using the mean beta estimate of all significant voxels extracted from the right amygdala. We found that the activation patterns across concentration were not different

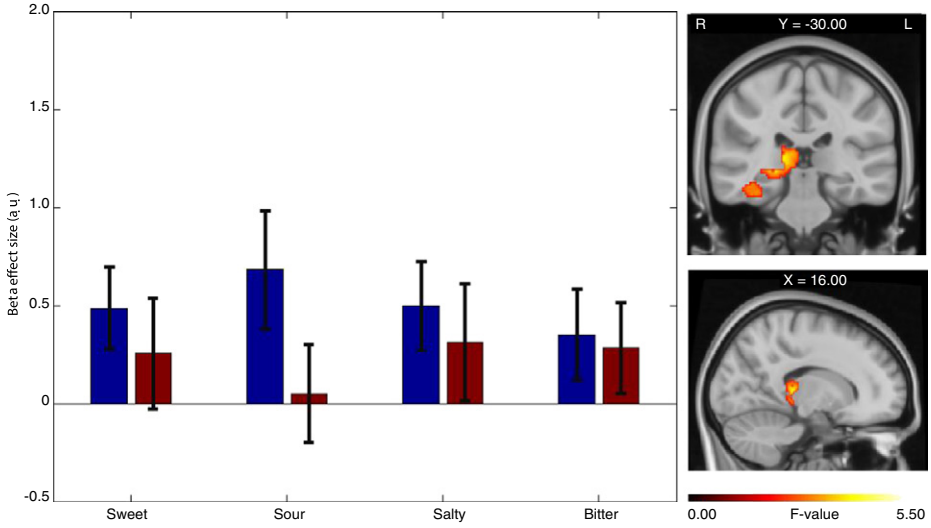

Fig. 4. Pulvinar nucleus of the thalamus. Bar graphs representing taste quality effects in young (blue) and older (red) participants.

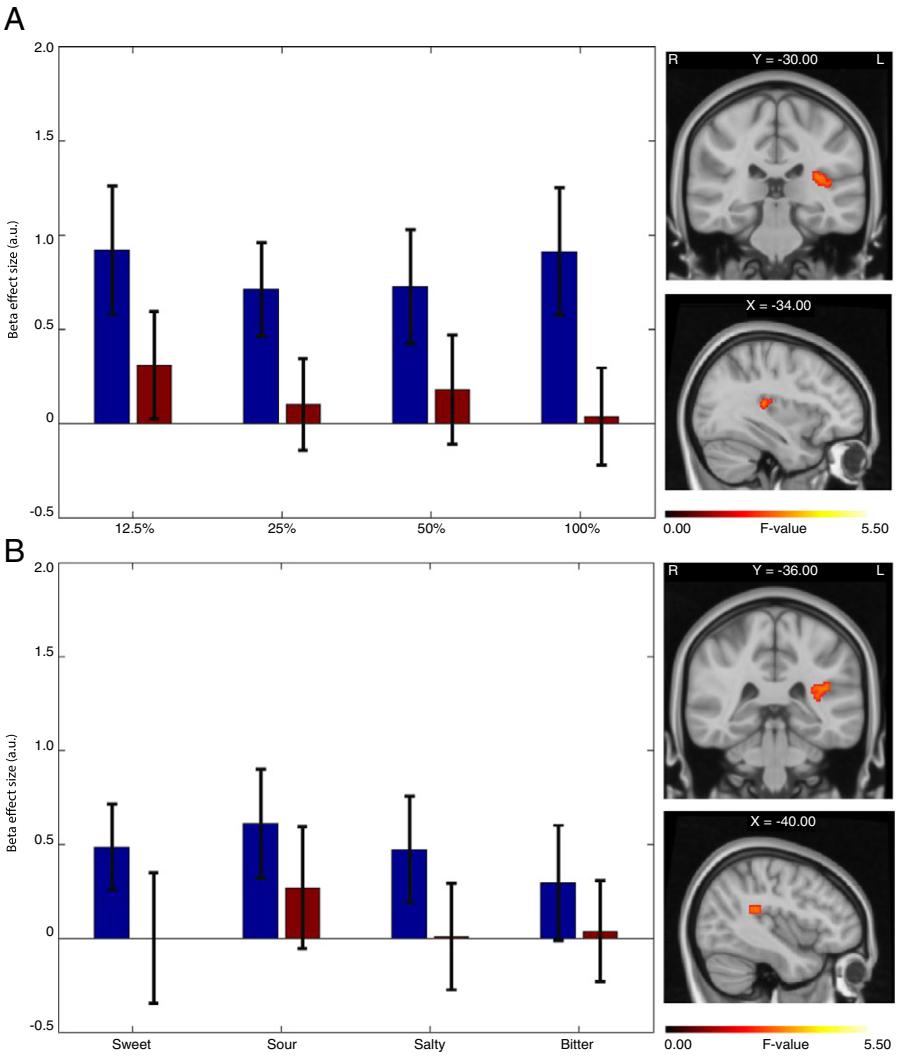

Fig. 5. Posterior insular cortex. Bar graphs representing A) taste concentration and B) taste quality effects in young (blue) and older (red) participants.

between young and older participants ($beta_{age:concentration} = 0.03$, n.s.), so the observed interaction effect between age and taste concentration seems to be dominated by the young adults showing more brain activation than older adults. In the left amygdala, we found that the response in the 12.5% taste concentration condition was significantly larger compared to the other taste concentrations in older adults (Fig. 9). In neither the right nor the left amygdala we observed differences between taste qualities, or an interaction between age and taste quality.

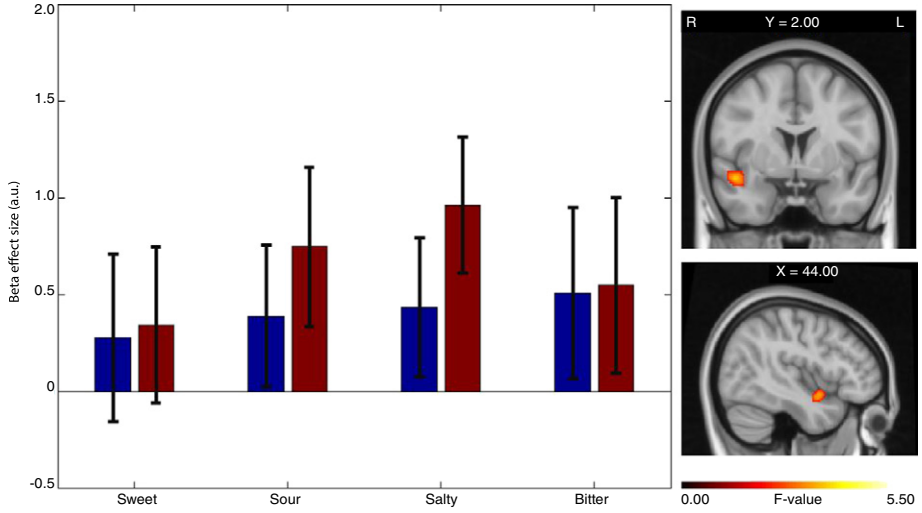

Fig. 6. Ventral anterior insular cortex. Bar graphs representing taste quality effects in young (blue) and older (red) participants.

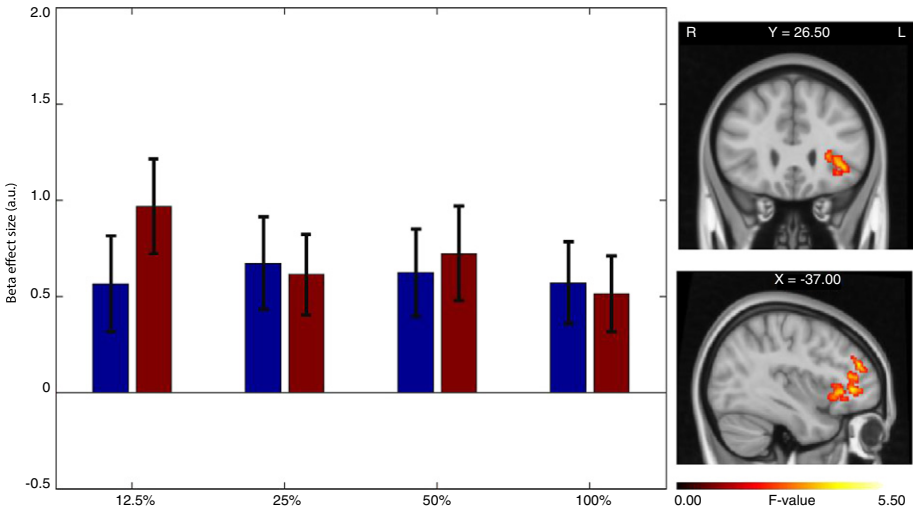

Fig. 7. Left dorsal anterior insular cortex. Bar graphs representing taste concentration effects in young (blue) and older (red) participants.

Reciprocal pathways from anterior insular cortex to the lateral hypothalamus

We found that activity in the lateral hypothalamus was different between taste concentrations (average ± SD [95% CI from bootstrap]: 12.5%: 0.64 ± 0.41, 25%: 0.43 ± 0.41, 50%: 0.45 ± 0.42, 100%: 0.15 ± 0.51), reflecting higher activation levels in the 12.5% concentration compared to the other concentration conditions. Age did not modulate these differences significantly. However, we did observe an interaction between age and taste quality in the lateral hypothalamus. Higher levels of activity in this area in young compared to older participants were most pronounced for the bitter, followed by salty, sweet, and sour taste quality (Fig. 10).

Pathways from the amygdala and hypothalamus–medio-dorsal nucleus of the thalamus

We observed enhanced activation in young compared to older adults in the medio-dorsal (MD) nucleus of the thalamus. No differences were found in this area between different taste qualities and taste concentrations; neither did age interact with taste quality or taste concentration.

Discussion

The role of the ageing brain in the processing of taste information has received little attention so far. Available evidence, however, demonstrate differential brain responses to taste stimuli of different taste qualities (Green et al., 2013; Haase et al., 2009; Jacobson et al., 2010) and also of different concentrations (Small et al., 2003). The mutual influence of both factors on age-related effects in taste perception still remains elusive. In the present study, we explicitly investigated the neural substrates underlying age-related effects on the perception of increasing concentrations of sweet, sour, salty, and bitter taste stimuli in healthy young and older adults.

We examined taste perception in individuals without reported taste disturbances. The overall taste scores based on psychophysical test scores indeed indicated that neither our young nor the older participants had a reduced ability to detect and identify sweet, sour, salty, or bitter substances, suggesting that age is not necessarily associated with differences in taste perception. Although previous studies showed that taste identification decreases with age (Fukunaga et al., 2005; Landis et al., 2009), our results indicated that there was no difference

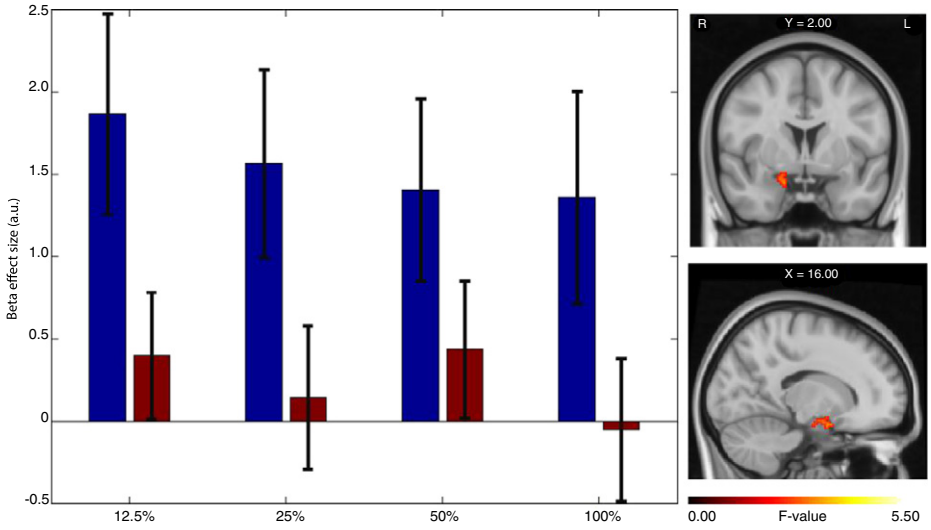

Fig. 8. Right amygdala. Bar graphs representing taste concentration effects in young (blue) and older (red) participants. Note that the maximum beta effect size on the y-axis is 2.5 instead of 2.0, as used in the other plots.

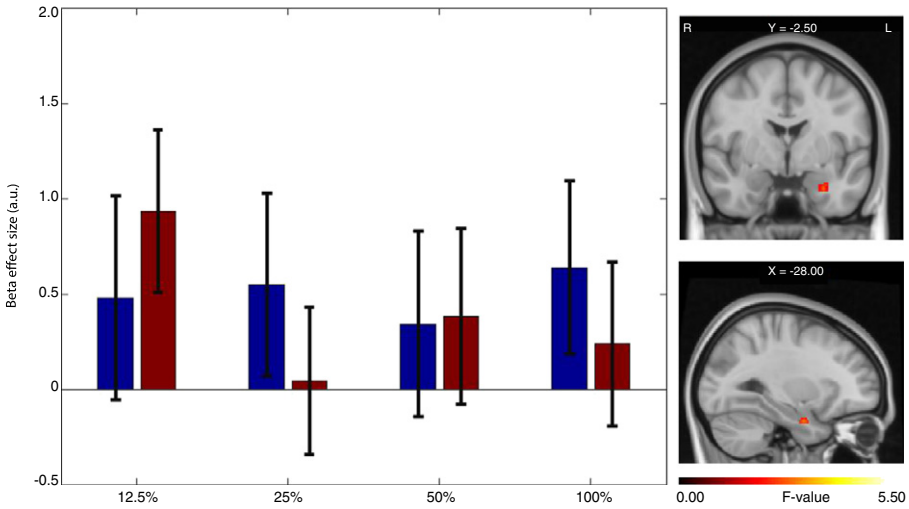

Fig. 9. Left amygdala. Bar graphs representing taste concentration effects in young (blue) and older (red) participants.

in taste detection performance between young and older persons within our participant group.

General age-related differences along the taste pathway

In order to investigate age-related differences in brain mechanisms underlying taste perception, we examined fMRI data recorded during tasting. After a taste is delivered in the mouth, information is passed on from the sensory system to the brain, where several brain areas are involved in the processing of different aspects of taste information ultimately leading to the perception of a taste. For reasons of clarity, we reported the findings in the order in which the brain areas appeared in the neural pathway involved in basic taste processing. We did not observe age group differences in brain activation in the first relay areas in the brain (i.e. the NTS and the ventral posteromedial nucleus of the thalamus), indicating that the taste information entering the brain in young and older adults do not seem to differ.

Age was found to define taste perception at higher levels in the taste pathway, especially in the primary and secondary somatosensory areas. We observed lower levels of brain activation in the older compared to young adults in these brain areas, and also in the pulvinar nucleus of the thalamus. The pulvinar nucleus of the thalamus receives either multisensory inputs from different sensory organs or projections from different sensory cortical areas (Cappe et al., 2009), and projects to the oral somatosensory areas on the postcentral gyrus and posterior insular cortex. These areas seem to play a key role in integrating taste and somatosensory inputs to produce a multisensory percept (Small and Prescott, 2005). Reduced brain activation in the somatosensory areas was previously found in older adults as compared to young adults in response to somatosensory stimuli (Brodoehl et al., 2013; Tomasi and Volkow, 2012), as well as in response to multisensory stimuli (Stephen et al., 2010).

The current study focused on individuals without hypogeusia, based on a screening using Taste Strips. Since detection and identification of a taste impregnated on the filter paper strips requires a judgement based on the subjective interpretation of (ambiguous) information, no clear distinction can be made between mechanisms (e.g. sensation, perception, and decision making) that underlie the verbal response. Taking this into account, we conclude that these results at least reflect the absence of changes in age-related difference in taste identification. Therefore, the observed lower levels of brain activation in the elderly might indicate that older adults, compared to young adults, need less

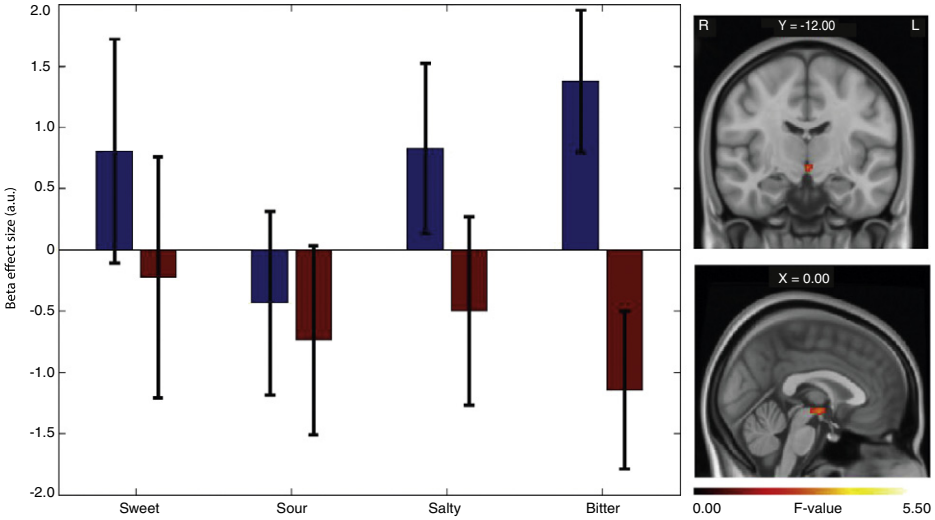

Fig. 10. Lateral hypothalamus. Bar graphs representing taste quality effects in young (blue) and older (red) participants.

brain activation to integrate (instead of detect and identify) both taste and somatosensory information.

Interpreting age effects on taste perception

Besides the above-mentioned brain areas, another pathway from the thalamus to the cortex might be involved in age differences in taste perception. The connection between the medio-dorsal nucleus of the thalamus and the dorsal anterior insular cortex was found to be involved in attending relevant stimuli (Buchsbaum et al., 2006). Several authors, proposing a role for the MD nucleus in attention, showed that enhanced levels of activation in this nucleus are needed for sustained attention, necessary to perceive different tastes (Plailly et al., 2008; Spence et al., 2001; Tham et al., 2009; Veldhuizen et al., 2011). In our study, we found that older adults showed lower brain activation in the MD nucleus, irrespective of taste concentration and quality, indicating that older adults may direct less attention to the taste stimuli as compared to young adults. Following this, we hypothesize that in order to adequately perceive the taste stimulus a more efficient reallocation of attention has to be realized by the older individuals. This indeed supported by the finding that the dorsal anterior insula was more activated in older adults in response to the unexpected (first) taste stimulus as compared to young participants. This finding is in agreement with Veldhuizen et al. (2012), who found that the dorsal anterior insular cortex was activated when participants received a sweet taste stimulus while they expected a tasteless stimulus, and attention had to be reallocated to perceive the taste.

Age and taste concentration

Age interacted with brain activation in response to different taste concentrations in the amygdala, irrespective of taste quality. The amygdala was previously found to interact with taste concentration (Anderson and Sobel, 2003; Small et al., 2003; Spetter et al., 2010), but the role of the amygdala in concentration coding was not always found to be straightforward (Winston et al., 2005). In our study, the interaction between age and taste concentration was dominated by higher levels of brain activation in young compared to older adults, especially in the right amygdala. It has been found that reduced activity in the right amygdala, particularly for negative stimuli, underlies differences in the perception of emotional stimuli in older adults (Roalf et al., 2011), while increased activity of the amygdala was associated with the processing of aversive tastes (Small et al., 1997). In addition, evidence for an interaction of taste concentration with taste pleasantness comes from two studies in which patients with amygdala lesions displayed increased intensity perception for aversive but not for pleasant tastes (Small et al., 2001a, 2001b). Our finding of increased activity in young adults could not be attributed to the perception of an aversive taste (e.g., the bitter taste quality), instead it seems to be related to liking ratings; young did report lower liking ratings as compared to the older adults in response to sweet and salty tastes. Therefore, the observed age-related differences in brain activation in the amygdala might represent its involvement in liking of tastes, which requires the integration of both concentration and pleasantness information related to a specific taste.

The mechanism underlying changes in taste perception in older adults is further complicated by the fact that the amygdala is an important site of neural habituation (i.e. decreased neural response after repeated exposure). Therefore, taste processing is inseparably linked to habituation. Previous studies showed changes in habituation in older adults (Dushanova and Christov, 2013; Vannini et al., 2012). For example, an fMRI study in which individuals repeatedly viewed neutral human faces indicated that the right amygdala shows greater habituation in young compared to older adults (Wedig, Rauch, Albert, Wright, 2005). The current findings merit further investigation and replication in future studies.

Age and taste quality

Besides the age-related differences in the perception of different taste concentrations, we studied whether basic taste processing showed quality specificity. Previous psychophysical studies indicated that the extent and significance of age-related differences in taste perception varies between taste qualities, but, as mentioned previously, this method does not provide insight in neural mechanisms underlying these differences. Neuroimaging does enable us to study functional activity in different brain areas, providing more information about specific processes involved in taste perception. It was previously found that young adults showed more activation in the thalamus and primary somatosensory area in response to sweet, sour, salty, and bitter tastes (Jacobson et al., 2010). In addition, more activation was found in the posterior insular cortex in response to sweet taste (Jacobson et al., 2010), but no age difference was found for bitter taste in this area (Green et al., 2013). However, these studies did not elaborated on the functional interpretation of the areas involved in terms of their particular roles within the taste pathway.

Individuals strive to maintain a stable metabolic state. This requires constant monitoring and adjustments to avoid imbalance by means of determining which foods to ingest and to avoid. To maintain metabolic homeostasis through food intake, the brain actively manipulates taste perception (Shin and Egan, 2010). Depending on the glucose, sodium, and acid levels in the individuals' body, the brain modulates the perceived intensity and pleasantness of a sweet, sour, salty and bitter taste, respectively (Tandon et al., 2012). For example, increase of leptin was related to a decrease of pleasantness ratings of sweet taste which in turn affects food intake, thereby playing an important role in regulation of glucose homeostasis (Sanematsu et al., 2009). In addition, after recovery from malnutrition, pleasantness of savoury solutions increased, thereby facilitating protein intake and homeostasis (Tsurugizawa, Uneyama, and Torii, 2014). Both the pulvinar nucleus and associated inferotemporal regions and the lateral hypothalamus play an important role in regulating homeostasis and appetite. Since we observed that young and older adults differ in their perception of different taste qualities especially in these brain areas, we hypothesize that age-related differences in the regulation of homeostasis underlie the quality specificity in taste perception.

In our study, age differentially affected the perception of sour, salty, and bitter tastes in two ways. First, older adults showed lower brain activation in the right pulvinar nucleus and associated inferotemporal regions in response to sour tastes as compared to young adults. It has been suggested that these brain areas are selectively modulated in a manner that reflects an individual's preference to maintain homeostasis (LaBar et al., 2001). Increased acidity in body tissue in older adults (Frassetto and Sebastian, 1996), was found to underlie decreased sour taste intensity perception. Second, older adults showed lower brain activation as compared to young adults in the lateral hypothalamus in response to salty and bitter tastes, and showed increased preference for salty but not bitter stimuli. This is in agreement with the finding that lesions in the lateral hypothalamus result in changes in salt preference (Abrão Saad et al., 2004; Da Silva et al., 1995). Based on our results, we consider that homeostatic mechanisms underlie taste quality specificity in age related differences in taste processing. Additional studies are needed to further test the hypotheses gathered from the current study.

Conclusion

The current study highlighted age-related differences in taste perception at the different higher order brain areas of the taste pathway. We found that taste information delivered to the brain in young and older adults did not differ, as illustrated by the absence of age effect in NTS and VPM activity. Our results indicate that multisensory integration changes with age; older adults needed less brain activation to integrate both taste and somatosensory information. Furthermore, older adults

seem to focus attention less efficiently to the taste stimulus; therefore attention had to be reallocated by the older individuals in order to be able to adequately perceive the tastes. In addition, we considered that the observed age-related differences in brain activation between taste concentrations in the amygdala reflect its involvement in processing both concentration and pleasantness of taste. Finally, we state the importance of homeostatic mechanisms in understanding the taste quality specificity in age related differences in taste perception.

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