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Changes in Taste Intensity Perception Following Anterior Temporal Lobe Removal in Humans

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Abstract

To investigate the role of the anterior temporal lobe in taste perception, we compared taste intensity estimations made by patients who had removal from either the left or the right anterior temporal lobe for the treatment of intractable epilepsy with a group of healthy control subjects. Estimations were made for five concentrations of each of four different tastes, as well as for five cards of varying saturations of gray, which served as a control task. A cross-modal magnitude estimation procedure was employed in which subjects used distance on a measuring tape to reflect intensity estimation. Distances were then transformed into logs, and the slope and the correlation with stimulus concentration or saturation was calculated. Correlation was taken as a measure of accuracy of estimation and slope was taken as a measure of perceived intensity. As predicted, repeated measures analysis of variance (ANOVA) revealed a significant difference between the control group and both patient groups in taste intensity estimations, but not for grayness, reflecting the importance of the anterior temporal lobe in low-level gustatory but not visual perception. Additionally, repeated measures ANOVA for slopes indicated that subjects in the right temporal group rated the bitter taste as more intense than did subjects in other groups, possibly reflecting increased intensity perception of the unpleasant bitter taste.

Introduction

Unlike audition and vision, which may be characterized as extrapersonal (Mesulam, 1998), the gustatory system has evolved a close relationship to the internal environment. This is reflected in the anatomical organization of the gustatory system. The primary gustatory cortex (PGA) is thought to be located in the heteromodal limbic cortex of the anterior insula/frontal-and-or-parietal operculum in human and non-human primates (Pribram and Bagshaw, 1954; Benjamin and Burton, 1968; Ogawa *et al*, 1985, Pritchard *et al*., 1986; Scott *et al*., 1986; Yaxley *et al*., 1990; Kinomura *et al*., 1994; Petrides and Pandya, 1994; Kobayakawa *et al*., 1999; Small *et al*., 1999a,b). Although the precise location is still debated, this region has strong connections to structures mediating autonomic responses such as the amygdala (Aggleton *et al.*, 1980) and has itself been implicated in autonomic functions (Penfield and Faulk, 1954; Tataranni *et al*., 1999). The secondary gustatory area (SGA) is likely located in heteromodal paralimbic cortex, in the caudolateral orbitofrontal cortex (CLOF) (Rolls *et al*., 1990; Rolls and Baylis, 1994; Baylis *et al.*, 1995; Small *et al*., 1997a, 1999a), which projects taste afferents to the lateral hypothalamus (Carmichael and Price, 1996).

In the traditional view of sensory organization, based upon studies of the extrapersonal senses, the primary cortical area denotes the first cortical representation of a sensory stimulus, where detection and sensation occur, while further processing leading to recognition of the stimulus is a function ascribed to secondary cortical areas. However, in a previous study (Small *et al*., 1997b) we reported deficits in taste quality recognition in patients who had surgical resection of the right anteromedial temporal lobe (AMTL), for surgical treatment of epilepsy, compared to patients with similar resection in the left hemisphere and a group of healthy control subjects. Thus, deficits in taste perceptual processing ensued from resection that did not infringe upon either of the cortical gustatory areas. Additionally, we used PET to measure regional cerebral blood flow evoked by tasting the same stimulus used in threshold assessment (citric acid) and observed activation in the right AMTL and SGA (Small *et al*., 1997b). Since the surgical treatment received by our patients likely entailed damage to this region of the temporal lobe, we proposed that the deficit in gustatory stimulus recognition resulted from disruption of functioning of this neural circuitry by the surgical procedure. Specifically, all surgical resections included at least four-fifths removal of the amygdala, a structure known to have taste-responsive cells (Scott *et al*., 1993; Yan and Scott, 1996), and the AMTL activity observed in the PET study

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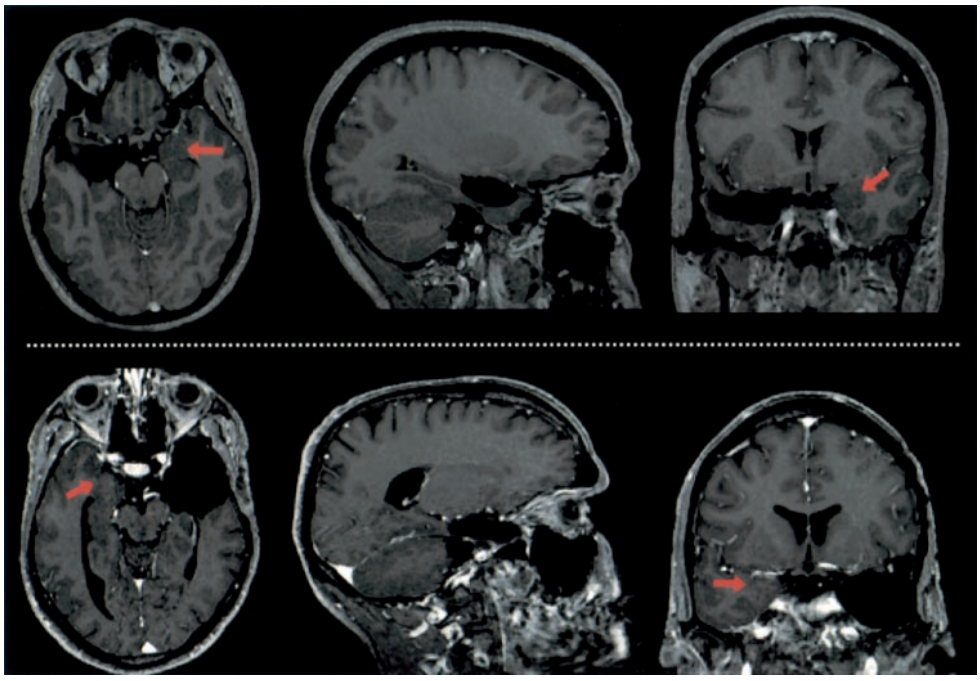

Figure 1 MRI scans illustrating representative resections. Arrows indicate the location of the amgydala in the intact hemisphere. Top row: slices from the postoperative MRI of a patient from the left AMTL group whose surgery did not include temporal neocortex. From left to right: horizontal, sagittal, and coronal sections. Bottom row: slices from the postoperative MRI of a patient from the right AMTL group, whose surgery included temporal neocortex. From left to right: horizontal, sagittal and coronal sections. Slices were selected to provide the optimal view of amygdaloid removal. The resections presented here are representative of all patients in this study and are typical of surgeries performed at the Montreal Neurological Institute for the relief of intractable temporal lobe epilepsy.

likely corresponded to the amygdala. Amygdaloid taste cells are not sensitive to quality of taste stimuli (Scott *et al.*, 1993). Rather, they are tuned to palatability (hedonic assessment of tastes) and are sensitive to concentration, one factor influencing palatability; they are thus thought to impart hedonic meaning to taste stimuli (Scott *et al.*, 1993; Nishijo *et al.*, 1998). We speculated that taste recognition involves integration of the gustatory code with motivational and affective networks related to feeding that are located within the AMTL (specifically the amygdala), a situation that differs markedly from traditional views of sensory organization.

The current investigation was designed to support and extend our previous findings. We assessed intensity estimations of gustatory and visual stimuli in patients with resection from the left or right AMTL and a group of healthy control subjects. The visual condition served as a control task to assess potential differences in scale use. All four classical taste stimuli (sweet, sour, salty and bitter) were used in the current study, whereas in our previous study we had used only a sour stimulus. Finally, in the present study we employed a suprathreshold intensity estimation task, developed by Weiffenbach *et al.* (Weiffenbach *et al.*, 1986), as opposed to a threshold assessment. We predicted similar performance in all three groups on intensity estimates of the visual stimuli, reflecting the independence of sensory versus affective processing of visual stimuli. In contrast, and in accordance with our previous results, we predicted deficits in estimation of concentration of the taste stimuli in patients with resection from the AMTL, reflecting the importance of these limbic structures, particularly the amygdala, in defining the gustatory code.

Table 1 Subjects

Group	*n*	Sex (F, M)	Mean age (range)	Mean IQ (range)	Smokers (*n*)
LT	12	6, 6	31 (17–48)	101 (82–135)	3
RT	16	8, 8	38 (22–52)	95 (78–126)	4
C	23	12, 13	33 (22–45)	not assessed	5

LT = left temporal; RT = right temporal; C = control.

Materials and methods

Subjects

Subjects were 28 patients at the Montreal Neurological Hospital who had undergone unilateral resection from the AMTL [12 from the left (LT) and 16 from the right (RT)] for the treatment of pharmacologically intractable epilepsy. All

patients had epilepsy arising from a single focus, determined by clinical pattern, electroencephalographic recordings and magnetic resonance imaging (MRI) scans. According to surgical reports, all patients had at least four-fifths of the amygdala and uncus removed, as well as partial resection of the hippocampus ranging in length from 1.5 to 4 cm. Varying amounts of the parahippocampal gyrus had also been removed, ranging in length from 0 to 5 cm. In addition, 21 of the 28 patients had had removal of temporal neocortex (LT = 8 of 12, RT = 13 of 16). In these patients the neocortical resections ranged between 4 and 6 cm along the first and third temporal gyri, with 3 cm resections in the second temporal gyrus (examples in Figure 1). Because the amygdala was the structure of interest for this study, the extent of amygdaloid resection was evaluated in postoperative MRI scans by an expert in volumetric MRI measurement. It was confirmed that in all cases there had been radical excision of the amygdala, comprising at least four-fifths of the total volume. All subjects gave informed consent according to the declaration of Helsinki (*Br. Med. J.*, 1991, 302, 1194) to participate in the study, which was approved by the Montreal Neurological Institute's Research Ethics Committee.

All patients were of normal intelligence, with a Full Scale IQ rating (Wechsler, 1981) of at least 75, and were left-dominant for language function, as determined by neuropsychological testing. A group of 23 healthy control subjects roughly matched to the patient group for age, sex and smoking habits constituted the control group (Table 1).

Materials

Taste stimuli were water and five concentrations each of sucrose, NaCl (both ranging from 1.8 to 5.6×10^{-2} M), quinine (ranging from 3.2×10^{-4} to 1.0×10^{-5} M), and citric acid (ranging from 3.2×10^{-2} to 1.0×10^{-3} M), making a total of six different stimuli in each taste category. United States Pharmacopoeia grade tastes mixed with double-distilled deionized water were used to make all solutions. The concentrations were selected according to their frequency of use in previous gustatory literature (Bartoshuk *et al.*, 1986; Weiffenbach *et al.*, 1986). All fluids were stored in 500 ml plastic narrow-mouth storage bottles at 4°C and brought to room temperature before use. The stimuli were presented as 5 ml of liquid in 30 ml plastic cups. A 150 ml plastic tumbler filled with double-distilled deionized water was available for rinsing between trials.

The shade cards were made from a computer-generated logarithmically valid progression of shading from white to black. This line of shade was divided into 12 sections. Every second section was mounted onto cardboard and subsequently laminated (Figure 2). A white card was the visual analogue of the water stimulus and a black card was the visual version of the most concentrated solution.

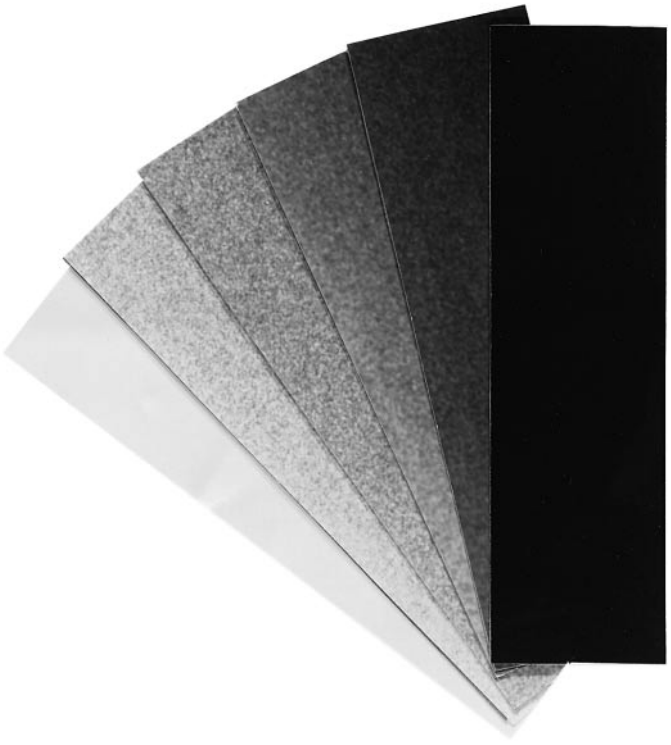

Figure 2 Visual stimuli (see Materials and methods section).

Procedure

A cross-modal magnitude-matching task developed by Weiffenbach and colleagues (Weiffenbach *et al.*, 1986) was used to assess the subjects' judgements of taste concentrations and saturations of gray. In this task, distance on a measuring tape was used to express perceived intensity. Subjects were presented with the blank side of the tape measure, which was mounted on a wooden platform, so that their response was unaided by numbers. However, the experimenter, sitting opposite the subject, was able to read the number side of the tape measure to record the distance of the response.

In each of four different taste tests, Subjects were presented consecutively with 12 cups containing the six different solutions (five concentrations of a single taste, plus a 'no-taste' water stimulus). The six solutions were presented twice (making a total of 12 cups for each taste) in pseudo-random order with the restriction that neither water nor the strongest concentration was presented first. The order in which the taste qualities were presented was counterbalanced across subjects. A visual test was interspersed between each taste quality test. In each visual test, six different visual stimuli were presented in pseudo-random order (five saturations of gray, plus a 'no gray' white stimulus). Subjects made an intensity estimate following the presentation of each visual stimulus. During the four taste tests, subjects were asked to sip the contents of the cup, swish the liquid around in their mouth and then expectorate in a sink. At this time they were asked to make their intensity

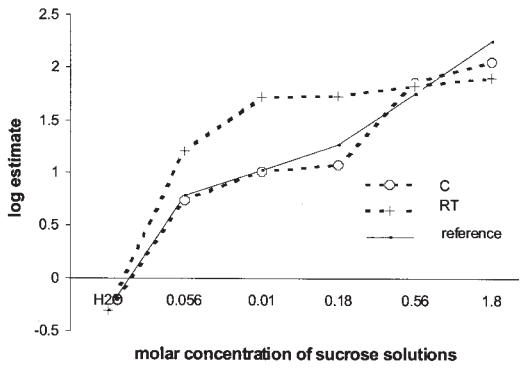

Figure 3 Representative sample data from two subjects depicting the difference in accuracy between RT and C groups. Log intensity estimate is represented on the *y* axis and the solutions ranging from water to the most concentrated solution are represented along the *x* axis (H_20, 0.056 M, 0.01 M, 0.18 M, 0.56 M and 1.8 M). The solid line is derived from the log transformation of the actual concentration of each solution. Water was assigned a value of 0.5 so that it could be converted into the log value depicted in the figure. The dotted line with circles depicts log transformations of intensity estimates made by a representative subject in the control group. The dotted line with crosses depicts log transformations of intensity estimates made by a representative subject in the RT group. The correlation between log intensity estimate and log stimulus concentration is 0.95 for the subject in the control group and 0.81 for the subject in the RT group

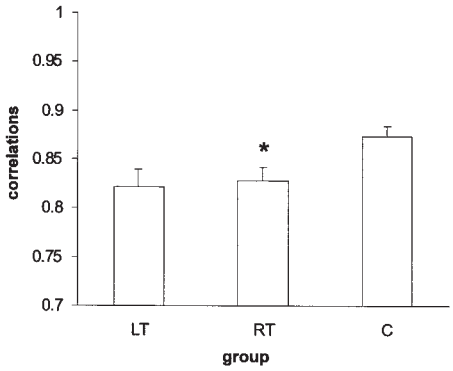

Figure 4 Mean scores of the LT, RT and control groups on the measure correlating taste intensity estimate and stimulus concentration. The RT group differs significantly from the control group, while the LT group just missed significance ($P = 0.06$).

judgement with the tape measure. Rinsing the mouth with double-distilled water was mandatory after tasting each solution.

Subjects were told that there would be six different stimuli for each category and that these would be presented twice. 'No taste' (i.e. water) and 'no gray' (i.e. white) were to be represented by zero distance on the tape. Distance was then to be assigned in proportion to the perceived intensity, such that a taste perceived as twice as strong should be assigned twice the distance. Before the testing began, subjects were reminded that for each category they should have six different distances corresponding to the six different stimuli. Only the results generated from the first two visual tests were used in the analysis so that there would be an equal number of data points for the visual and gustatory data.

Data analysis

Following the procedure outlined by Weiffenbach *et al.* (Weiffenbach *et al.*, 1986), all raw data were transformed into log values to standardize the responses. All zero responses (no distance) were assigned the value of 0.5 (including water) so that a log transformation would be possible. All data points were included in all analyses. For each subject the slope and the correlation between stimulus concentration (or saturation) and intensity estimate (assigned distance) were calculated for each taste quality. This same procedure was followed for the visual stimuli. Slope provided a measure of perceived intensity difference between each concentration for a given stimulus, and the correlation provided a measure of the accuracy of subjects' perception of intensity compared to actual concentration or saturation. Repeated measures analyses of variance (ANOVA) were then carried out for both slope and correlation. Separate one-way ANOVAs were conducted for the visual stimuli. Visual and taste tests were not analysed together in the main analyses because we wanted to look at potential differences in intensity estimates made to the different tastes. However, to determine if performance on the visual and gustatory tasks was equivalent in the control group (i.e. if the tasks were equivalent), a repeated measures ANOVA was also carried out comparing the correlations between intensity estimate and stimulus concentration for each of the four taste qualities with the estimates of the saturation of gray.

Results

For the control group there were no significant differences between the accuracy of intensity estimates made for the concentrations of the tastes compared to the intensity estimates made for the saturations of gray [$F(4,22) = 1.06$, $P = 0.38$]. This result indicates that the control subjects were as accurate at reflecting the intensity of taste concentration as they were at reflecting the intensity of the saturation of gray, and therefore suggests that the visual and gustatory tasks were equivalent in difficulty.

A main effect of group [$F(2,48) = 5.32$, $P = 0.008$] was observed for correlations derived from the gustatory intensity estimates. This result was pursued with Tukey's HSD test for unequal means, which revealed that the RT group differed significantly from the control group (RT: $P = 0.05$). The LT group's performance, compared to the control group, just missed significance (LT: $P = 0.06$). Figure 3 shows an example of raw data from two cases and Figure 4 shows the main effect of group. No group by taste interaction was observed [$F(2,48) = 0.67$, $P = 0.67$], indicating that there were no differences between the groups on the individual taste tests.

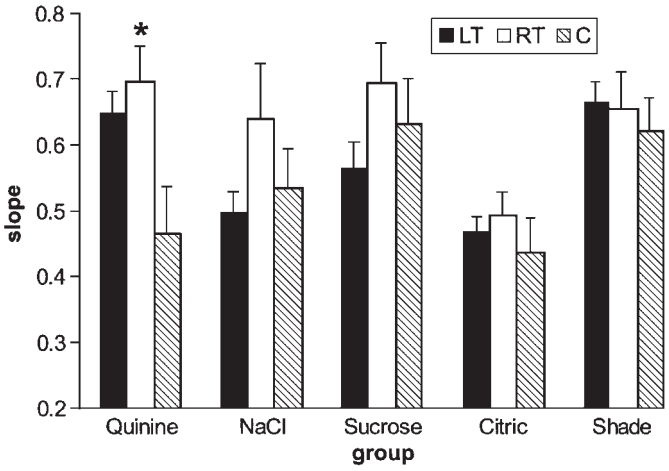

Figure 5 Mean slopes of the LT, RT and control groups for the taste intensity ratings each of the four tastes and the shades. The RT group differs significantly from the control group on the quinine intensity estimate. No other significant differences were present for the groups. However, citric acid was rated significantly less intense than all other tastes except NaCl ($P = 0.07$).

Analysis of the slopes revealed a main effect of group [$F(2,48) = 3.8$, $P = 0.03$] and a group by taste interaction [$F(6,48) = 2.5$, $P = 0.02$]. *Post-hoc* analyses (Tukey's HSD) indicated that the only group difference was between the RT and control groups for quinine ($P = 0.000$; Figure 5). Specifically, the slopes produced by the intensity estimates for quinine made by subjects in the RT group were consistently steeper than the slopes produced by the intensity estimates for quinine made by the subjects in the control group. The LT group did not differ significantly from the RT ($P = 0.18$) or the C group ($P = 0.12$) in this comparison.

A main effect of taste was also present [$F(4,48) = 7.4$, $P = 0.000$]. Pairwise comparisons, with Bonferroni correction for multiple comparisons, revealed that the difference was due to lower slopes produced by intensity estimations of citric acid compared to all other tastes ($P < 0.001$ for comparisons with sucrose and quinine and 0.07 for NaCl; Figure 5). The lower slope means that subjects found citric acid less intense than the other tastes.

Finally, as predicted, two separate one-way ANOVAs showed that there was no main effect for group for the correlations [$F(2,48) = 0.49$, $P = 0.61$] or slopes [$F(2,48) = 0.27$, $P = 0.77$] produced by the shade intensity estimates. Thus, performance on the visual task was equivalent across the groups for both measures (slope and correlation).

In summary, according to our definition whereby correlation is a measure of accuracy of estimation and slope is a measure of perceived intensity, both patient groups were less accurate than the control group at estimating intensity of taste (although the difference between LT and control groups just missed significance ($P = 0.06$) and subjects in the RT group perceived the quinine to be stronger than did subjects in the control group. Additionally, a similar analysis with the visual data showed that there were no differences between the performance of the patients and the control group.

Discussion

Patients with excision from either left or right AMTL were less accurate at estimating taste intensity than was a matched control group. This result is unlikely to be due to deficits in the ability to use distance to reflect intensity perception *per se*, because the patient groups were not different from the control group at using the same method to represent the saturation of gray in a matched visual task. We propose that the difference between the patient and control groups reflects deficits in taste intensity perception produced by removal of the AMTL. This result is in accordance with previous gustatory psychophysical studies in patients with AMTL resection (Henkin *et al*., 1978; Small *et al*., 1997b) in suggesting that the AMTL is important for gustatory perception. These studies reported elevated recognition thresholds for a sour taste in patients with excision from the AMTL. The AMTL has also been implicated in human gustatory processing by neuroimaging studies (Small *et al*., 1997a,b; Zald *et al*., 1998; Francis *et al*., 1999).

Projections to the amygdala from both primary (Turner *et al*., 1981) and secondary taste cortices (Amaral and Price, 1984; Baylis *et al*., 1995), as well as from the subcortical medullary taste nucleus (Norgren, 1974; Price, 1981), have been elucidated in monkeys, and single-cell recording studies in the macaque have identified amygdaloid neurons that respond to gustatory stimulation (Nishijo *et al*., 1988a,b, 1998; Scott *et al*., 1993, Yan and Scott, 1996). While these taste-responsive neurons do not provide an adequate neural basis for the discriminative capacity of humans or monkeys with regard to stimulus quality, the cells are sensitive to concentration (Scott, 1992), which is one determinant of palatability (Kocher and Fisher, 1969). It has thus been suggested that the primate amygdala contributes to gustatory processes by imparting hedonic appreciation and emotional significance to taste experiences (Scott *et al*., 1993). Electrophysiological data collected in the rat amygdala support this hypothesis, as the neural response to taste stimuli has been shown to be driven by taste stimulus palatability (Nishijo *et al*., 1998). Specifically, they found a greater number of taste cells that responded to bitter, which is characteristically aversive, in the amygdala compared to in other levels of the gustatory neuroaxis. Second, they report higher correlation coefficients between the response evoked by tastes with similar affective valence than at other levels of the gustatory neuroaxis. Neuroimaging studies in humans also suggest that hedonic evaluation of taste is related to amygdaloid function. Small and colleagues (Small *et al*., 1997a) reported amygdala activation during presentation of unpleasant compared to pleasant combinations of tastes and smells, and

Zald and colleagues (Zald *et al.*, 1998) reported amygdala activation during aversive compared to neutral and pleasant gustatory stimulation.

Taste neurons in the primary gustatory area (PGA) are sensitive to both quality and concentration (Smith-Swintosky *et al.*, 1991; Scott and Plata-Salaman, 1999). We have previously suggested that while taste sensation may occur in the PGA, recognition involves integration of the gustatory code with motivational and hedonic networks related to feeding located within the AMTL, thus accounting for elevated recognition thresholds following ATL removal (Small *et al.*, 1997b). Given the results of the current study, we propose an extension of this hypothesis to include intensity perception. Specifically, normal taste intensity perception emerges as a function of integrated processing between sensory taste cells in the PGA and hedonic taste cells in the amygdala.

In the present study, we also found that patients in the right AMTL group generated a steeper slope than the slope generated by control subjects for the bitter quinine stimulus. This suggests that subjects with resection from the right AMTL found the bitter stimulus more intense than did the control subjects. However, taste stimulus concentration is related to both intensity perception and palatability. For example, Kocher and Fisher (Kocher and Fisher, 1969) reported that tastes perceived as unpleasant tended to receive higher ratings of intensity. Conversely, motivational factors such as satiety can influence intensity perception. For example, Giza and Scott (Giza and Scott, 1987) showed that injection of a glucose load reduces perceived sweetness intensity in rats. Thus, it is difficult to dissociate intensity perception from motivational factors such as perceived aversiveness. Consequently, it is possible that the steeper slopes observed here reflect an altered hedonic appreciation of taste, an increased intensity perception for bitter, or both. If this result does reflect a hedonic change, it would be consistent with the results of an experiment by Touzani and colleagues (Touzani *et al.*, 1997), showing increases in the aversive value of quinine following bilateral ibotenic acid lesions to the central amygdaloid nucleus in the rat. We must emphasize that in the current study we did not test our subjects for genetic variations in taste intensity perception. There are at least three phenotypic variations in taste intensity perception that occur in the general population (Bartoshuk *et al.*, 1994). People can be classified as non-tasters, tasters and super-tasters by asking them to rate the intensity of bitter tasting 6-*n*-propylthiouracil (Bartoshuk *et al.*, 1994). Correlations have been established between 'taster-status' and taste bud density (Miller and Reedy, 1990), and it is likely that variations in taste bud density result in differences in taste intensity perception for a variety of tastes (Bartoshuk *et al.*, 1998). Since we did not evaluate taster-status, it is possible that there were more super-tasters in the right ATL group. Thus, we must interpret this result with caution. However, 12 of the 17 patients in this group had also participated in our citric acid threshold experiment (Small *et al.*, 1997a) and were shown to have normal detection thresholds. Presumably, a preponderance of super-tasters in this group should have resulted in a mean decreased taste threshold (super-sensitivity). We have subsequently replicated this result, taking into account individual differences in genetically determined taster status (Small *et al.*, 1999b).

In conclusion, we report deficits in intensity estimation for taste but not visual stimuli following removal of the AMTL in human subjects. This result is in accordance with our previous study, and suggests that sensory and affective processing of taste are highly integrated. We propose that normal taste quality recognition and taste intensity perception emerge as a function of the integration of sensory processing in the PGA and affective processing in the amygdala. The suggestion that the AMTL is important for gustatory sensory processing marks a departure from classical notions of sensory organization, in that it implies that limbic structures partake in sensory perception in the gustatory modality. This departure is highlighted by the dissociation of visual from gustatory task performance observed here.

There are several reasons why the integration of sensory and affective processing is adaptive in the gustatory system. The sense of taste has very little to do with food identification, which is usually accomplished by the olfactory and visual systems, before food is introduced to the mouth. Rather, the purpose of taste perception is to aid in an affective judgement about whether to accept or reject the food. As such, the sense of taste has been described as the 'gatekeeper' of our internal environment (Scott, 1992). Moreover, taste is not only a sensory stimulus, but also a primary reinforcer. For example, newborns will react to bitter tastes with facial expressions of disgust and to sweet tastes with contented facial expressions, and thus it is thought that the affective response to taste is innate (Steiner, 1979). This affective 'hardwiring' saves us from the peril of having to learn that bitter signifies the presence of poison.

Finally, subjects with resection from the right AMTL rated the bitter stimulus as more intense than did subjects in the other groups, suggesting that the aversiveness of bitter is potentiated as a result of the surgery. Further research is warranted to understand the mechanism underlying this affective change. It is noteworthy that although the two patient groups did not differ statistically from one another ($P = 0.18$), the effect was relatively greater for the RT compared to the LT group. This is consistent with other reports in the literature of right hemisphere predominance in taste (Small *et al.*, 1997a,b, 1999a,b; Zald *et al.*, 1998; Francis *et al.*, 1999).

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