



Increased taste intensity perception exhibited by patients with chronic back pain

Dana M. Small^{a,b,c}, A. Vania Apkarian^{d,e,f,*}

^a *The John B Pierce Laboratory, Yale University, New Haven, CT, USA*

^b *Department of Surgery, Yale University, New Haven, CT, USA*

^c *Department of Psychology, Yale University, New Haven, CT, USA*

^d *Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

^e *Anesthesia, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

^f *Neuroscience Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

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Abstract

There is overlap between brain regions involved in taste and pain perception, and cortical injuries may lead to increases as well as decreases in sensitivity to taste. Recently it was shown that chronic back pain (CBP) is associated with a specific pattern of brain atrophy. Since CBP is characterized by increased sensitivity to pain, we reasoned that the sense of taste might also be enhanced in CBP. Detection and recognition thresholds were established for a sour taste and ratings of both suprathreshold taste intensity and pleasantness–unpleasantness perception were collected for sweet, sour, salty and bitter stimuli in 11 CBP patients and 11 matched control subjects. As a control, ratings were also collected for visual assessment of degree of grayness. There was no difference between CBP and control subjects for visual grayness rating. On the other hand, CBP patients in comparison to control subjects rated gustatory stimuli as significantly more intense but no more or less pleasant and showed a trend towards a lower detection threshold (i.e. increased sensitivity). The selectivity of the taste disturbance suggests interaction between pain and taste at specific brain sites and provides further evidence that CBP involves specific brain abnormalities.

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1. Introduction

Studies examining brain responses to taste have reported activation of the entire extent of the insula and overlying frontal, parietal and temporal operculum, the anterior cingulate cortex, amygdala and orbitofrontal cortex, e.g. (Faurion et al., 1999; Kinomura et al., 1994; O'Doherty et al., 2001; Small et al., 1999, 2003). Many of these same

regions are activated in response to pain, see reviews (Apkarian et al., 2005; Derbyshire, 1999; Peyron et al., 2000; Price, 2000; Treede et al., 2000), suggesting that taste and pain share overlapping neural substrates. Yet the interaction between pain and taste has remained essentially unexplored, although see (Formaker and Frank, 2000).

Gustation and chronic back pain (CBP) also appear to have overlapping neural circuits. Baliki and colleagues used fMRI to identify brain activity related to spontaneous fluctuations of ongoing CBP (Baliki et al. Society for Neuroscience Abstract 2003, manuscript in preparation). They found that activity in the anterior insula increased in phase with spontaneous pain and could explain >80% of the variance of duration of CBP. The anterior insula receives gustatory information from the taste thalamus (Pritchard

Abbreviations: CBP, chronic back pain; DTh, detection threshold; LMS, labeled magnitude scale; PROP, 6-*n*-propylthiouracil; RTh, recognition threshold.

* Corresponding author. Address: Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA. Tel.: +1 312 5030404; fax: +1 312 5035101.

E-mail address: a-apkarian@northwestern.edu (A.V. Apkarian).

et al., 1986) and is considered a core gustatory region, which is sensitive to stimulus intensity in primates (Scott and Plata-Salaman, 1999) and humans (Small et al., 1999, 2003).

Interestingly, lesions to the insula, as well as other parts of the gustatory system, may lead to increases as well as decreases in taste sensitivity (Mak et al., 2005; Pritchard et al., 1999). For example, Mak and colleagues (Mak et al., 2005) describe increased taste and smell sensitivity in a patient with a unilateral insular lesion. Similarly, patients with unilateral resection from the anteromedial lobe, including the amygdala, have been shown to lead to elevated ratings of taste intensity (Small et al., 2001a,b). In rodents, increased taste reactivity, a measure of perceived stimulus intensity and saliency, has also been observed following removal of the thalamus (Grill and Norgren, 1978) or amygdala (Touzani et al., 1997). Thus, increases in taste intensity perception are common following central lesions. A recent study in humans demonstrated that CBP is associated with brain volume and regional density decreases in the thalamus and prefrontal cortex (Apkarian et al., 2004b). Given that CBP is by definition associated with increased sensitivity to pain and that increased taste intensity responses have been observed following lesions to regions that appear dysfunctional in CBP, we reasoned patients with CBP, who have ongoing spontaneous pain, would also exhibit increased taste intensity perception without manifesting changes in visual intensity ratings because of a lack of overlap between brain representation for pain and vision. We further reasoned that if heightened sensitivity could be demonstrated at the threshold level, then any change in sensory perception likely reflects enhanced sensation as opposed to a bias to select higher ratings.

2. Materials and methods

2.1. Subjects

Subjects were 11 patients with CBP and 11 age, gender, and education matched control volunteers. Candidates were screened by telephone interview for history of back pain, handedness, and self-reported history of medical, neurologic and psychiatric illness (see Table 1).

Patients fulfilled the International Association for the Study of Pain (IASP) criteria for CBP (Merskey and Bogduk, 1994) and were diagnosed in accordance to recent guidelines (Deyo and

Weinstein, 2001). Diagnosis was performed by experienced clinicians based on history, general physical exam, and detailed neurological exam, especially sensory, motor, reflex and gait examinations. Briefly, all CBP patients had unrelenting pain for more than one year, primarily localized to the lumbosacral region, including buttocks and thighs, with or without pain radiating to the leg. Some CBP patients also indicated presence of pain outside this region, for example upper back. If so, they were considered CBP only if the main source of pain was lumbosacral. We did not distinguish as to the source of CBP, which may be due to various etiologies, like fracture, inflammatory joint disease, post-surgical, combinations of these, or idiopathic (Deyo and Weinstein, 2001). The clinical data indicated that one of 11 patients had primarily musculoskeletal diagnoses, five had pure radiculopathy, and five had a mixture of musculoskeletal and radiculopathic pain. Patients with CBP were not included in the study if they had high levels of anxiety or depression (>40 on the Beck's Anxiety or Depression Indices; (Beck and Steer, 1993a,b) or if they used large amounts of medications (>3 categories of analgesics; details regarding use of medications were not documented and we did not interfere with patients' medication use). Healthy age- and gender-matched control subjects were recruited via advertisement, phone solicitation and acquaintance. Anxiety (Beck's Anxiety Index, (Beck and Steer, 1993b), depression (Beck's Depression Index, (Beck and Steer, 1993a), and properties of pain (Short-form of McGill Pain Questionnaire, (Melzack, 1987) were documented with questionnaires. Anxiety, depression and pain ratings (Table 1) were in the reported range for back pain patients (Apkarian et al., 2004a; Grachev et al., 2001, 2002), and anxiety and depression were statistically not different between patients and normal subjects (t -test, $P>0.05$).

There is significant individual variation in sensitivity to taste in the normal population that is related to the number of taste receptors on the tongue and perceived intensity to the substance 6-*n* propylthiouracil (PROP) (Bartoshuk, 2000; Lucchina et al., 1998). Subjects were therefore, matched for their ability to taste PROP to insure that our CBP and control groups were matched for overall sensitivity of the peripheral gustatory mechanisms. Age and PROP intensity rating were compared across the groups using an ANOVA. There were no group differences in either age ($F_{1,20}=0.003$; $P=0.95$), or PROP intensity ratings ($F_{1,20}=0.26$; $P=0.87$) (Table 1).

2.1.1. Taste solutions

For threshold estimation, UPS grade citric acid was mixed with double-distilled deionized water to make solutions ranging in concentration from 1.0×10^{-2} to 1.0×10^{-7} M. Citric acid was chosen for two reasons: (1) to reduce individual differences in detection attributable to diet (i.e. people who use more salt are less sensitive to salt), and (2) we have previously successfully used citric acid (Small et al., 1997a). For suprathreshold whole mouth

Table 1
Demographic information

Group	<i>n</i>	Gender (male, female)	Age (years)	Education (years)	Depression	Anxiety	Pain Sf-MPQ	PROP rating
Controls	11	5M, 6F	46.3 [27–70]	14 ± 4.8	11.4 ± 3.7	11.0 ± 3.5		18.2 [0–50]
CBP	11	5M, 6F	46.2 [27–71]	16.1 ± 0.7	11.9 ± 4.2	16.7 ± 5.3	24.9 ± 6.8	16.9 [0–53]

Mean and range [] or standard error of the mean (±) are shown. Education is number of years of schooling, starting from first grade. Depression and anxiety use Beck's Anxiety and Depression Indices (Beck and Steer, 1993a,b). Pain is derived from short-form of McGill Pain Questionnaire (Melzack, 1987).

stimulation, solutions were the same as those used in our previous studies sweet = 1.0 M sucrose, salty = 1.0 M NaCl, bitter = 0.001 M quinine hydrochloride and sour = 0.032 M citric acid (Small et al., 2001b). The solutions were made with UPS grade chemicals mixed with double-distilled deionized water. Q-tips were used to apply the solutions onto the tongue to achieve discrete locus stimulation according to the procedure outlined by Prutkin and colleagues (Prutkin et al., 2000). For whole mouth stimulation, solutions were presented as 5 ml in a 10 ml disposable plastic cup. A 150 ml glass tumbler was available for rinsing between trials.

2.1.2. General-labeled magnitude scale (g-LMS)

Taste intensity perception was assessed via ratings made on the g-LMS, a semantic scale of perceptual intensity characterized by quasi-logarithmic spacing of its verbal labels (Green et al., 1996). A laminated photocopy of the g-LMS was placed in front of the subjects so that they could make their rating by crossing the scale with a mark made with a water-soluble marker. The LMS has been shown to yield ratio-level data comparable with those produced by magnitude estimation (Green et al., 1996). A transparency was made of the LMS with a ruler that divides the scale into 100 units. This numerical scale was superimposed on the laminated scale after each trial to ascertain the numerical value associated with the point marked by the subjects.

2.1.3. Affective scale

Ratings of stimulus pleasantness and unpleasantness was made using a 21-point scale with 0 = neutral, +10 = extremely pleasant, and -10 as extremely unpleasant.

2.1.4. 6-n-Propylthiouracil (PROP) papers

PROP papers were made according to the procedure outlined by Bartoshuk and colleagues (Bartoshuk et al., 1994). Five grams of PROP was added to 500 ml of boiling tap water to make a saturated solution. Circles (3 cm in diameter) were cut from Whatman 1 filter paper and dipped into the solution until they were completely soaked. The papers were then allowed to dry and stored for use.

2.1.5. Varying saturation of gray visual stimuli

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. A white card was the visual analogue of the water stimulus and a black card was the visual analogue of the most concentrated solution. Subjects rated the grayness on a modified g-LMS.

2.1.6. Procedure

Detection thresholds A modified staircase method was used to establish detection thresholds (Doty et al., 1994) as previously described in (Small et al., 1997b). On each trial, two cups containing liquid were presented. One contained water plus citric acid and the other just water. Subjects sipped both cups, fully swishing each in the mouth before expectorating, and then indicated which cup contained a taste other than water. Subjects were asked to make the judgment after tasting both solutions. If the response was incorrect, on the next trial a higher concentration of the citric acid solution was presented. If the response was correct, the same concentration was presented a second time. If the subject responded correctly a second time, the concentration of citric acid

was lowered for the next trial. A change in direction from increasing concentrations to lowering them, or vice versa, constituted a reversal. Eight reversals were obtained to complete the test. Concentrations for the last four reversal points were averaged to determine the detection thresholds. Subjects were told that if at any time they knew what taste they were sipping, they should inform the experimenter; however, no feedback was given until the end of testing. Once the detection threshold was determined, subjects were asked whether they could identify the taste they had been sipping. If they did, or if they had correctly identified the taste during the detection threshold testing, the concentration at which they informed the experimenter of the taste quality was taken as their recognition threshold. All other subjects were given cups of increasing concentration until they could recognize the taste. The highest concentration given during the detection threshold examination was used as the starting point. Various responses were considered correct as long as they resembled a sour drink (i.e. 'sour,' 'grapefruit,' 'lemon'). The concentration at which each subject gave a correct response was taken as the recognition threshold.

Assessment of suprathreshold taste intensity and pleasantness: suprathreshold taste intensity and pleasantness perception were evaluated after thresholds were established. Subjects were presented twice with the four tastes as 5 ml solutions in 30 ml plastic cups. Order of stimulus presentation was counterbalanced across subjects, with the exception that the bitter solution was always presented last and therefore rated twice in a row. Subjects were told that there would be four different tastes and that they would be presented twice in no particular order, except that the bitter taste would be presented last. Subjects were asked to sip the entire solution, hold it in their mouths for several seconds, and then expectorate. Intensity ratings were made using the g-LMS and pleasantness ratings were made with the affective scale immediately following expectoration. Subjects then rinsed twice before tasting the next solution.

Ratings of the visual stimuli: following taste testing, subjects were instructed to use a modified g-LMS to rate the saturation of each of the six visual stimuli. They were told that white = 0 and the blackest black they could imagine represented 100. Order of presentation was randomized and each card was shown twice. Subjects were told that there were six cards and that each would be presented twice in no particular order. The average rating was used for statistical analysis.

Determining PROP-taster status: finally, subjects were presented with the PROP filter paper and told that it contained a taste. Subjects then placed the whole piece into their mouths and let it moisten with saliva. When the perceived taste was at its maximum (after about 5–10 s), subjects rated the intensity using the g-LMS.

3. Results

3.1. Gustatory thresholds

Two ANCOVAs were performed with PROP ratings as a covariate, one for detection thresholds and one for recognition thresholds. There was a trend towards a main effect of group for detection thresholds ($F_{1,19} = 2.1$; $P = 0.08$), with CBP patients displaying lower thresholds than

controls (mean CBP=0.00005 and control=0.00012) (Fig. 1). In other words, as predicted, the CBP patients tended to be more sensitive to taste at threshold level. A similar analysis for the recognition thresholds did not reveal group differences ($F_{1,19}=0.003$; $P=0.95$).

3.2. Suprathreshold intensity and pleasantness estimation of taste

Intensity ratings on the g-LMS and pleasantness ratings on the affective scale were analyzed separately with repeated measures ANCOVA using PROP rating as a covariate of no interest. As predicted, the CBP patients rated the taste stimuli as significantly more intense than the control subjects (main effect of group $F_{1,20}=4.6$; $P=0.02$) (Fig. 2). There was also a main effect of taste ($F_{1,20}=8.3$; $P=0.0001$), produced by significantly higher ratings for bitter and salty solutions compared to the sweet solution ($P=0.003$ and 0.02 , respectively) and sour solution ($P=0.001$ and $P=0.03$) (mean rating for bitter=32.3, salty=28.9, sweet=24.3, and sour=24.2). There was no taste by group interaction ($F_{1,20}=0.46$; $P=0.51$). Planned comparisons, corrected for multiple comparisons, revealed that the lack of interaction reflected the fact that the CBP group rated the sweet, sour, and salty tastes as significantly more intense than the control group (sweet $P=0.03$, salty $P=0.04$, sour $P=0.01$ and see Fig. 2). A similar relationship was observed for bitter, though it was only a trend ($P=0.12$). The lack of interaction indicates that the smaller group difference in bitter ratings does not reflect differential group intensity ratings of this stimulus compared to the three other tastes.

In contrast to the significant group differences in intensity, no group differences were observed for pleasantness ratings ($F_{1,20}=1.3$; $P=0.27$). Nor did we observe a group by taste interaction ($F_{1,20}=0.38$; $P=0.77$). There was, however, a main effect of taste ($F_{1,20}=23.9$; $P<0.001$). Examination of planned pairwise comparisons showed that sweet was significantly more pleasant

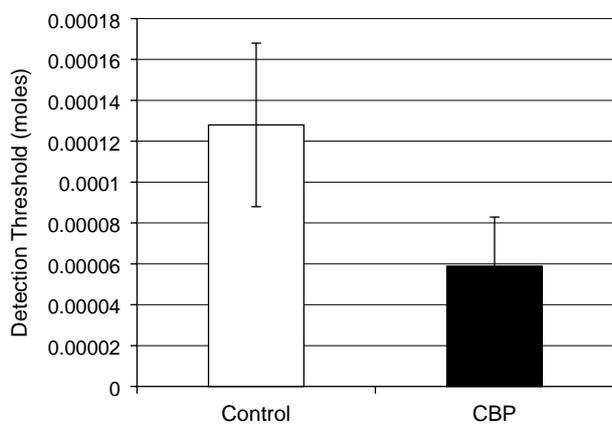


Fig. 1. Mean detection threshold for citric acid in Control and chronic back pain (CBP) subjects. Error bars represent standard error of the mean.

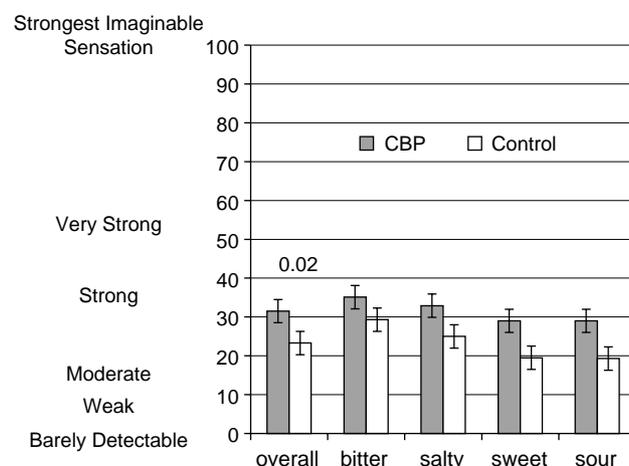


Fig. 2. Mean and standard errors of the mean (error bars) for intensity ratings on the general labeled magnitude scale (y-axis) collapsed across all tastes (overall) and for each of the four tastes (x-axis). Data are shown separately for Control and chronic back pain (CBP) subjects.

compared to all other tastes (largest $P<0.001$) and bitter significantly more unpleasant compared to all other tastes (largest $P<0.005$) (Fig. 3).

3.3. Visual stimuli

An independent sample *t*-test was performed on the slopes of the saturation ratings of the gray shade cards that were made on the modified g-LMS. The groups did not differ significantly ($t_{1,20}=0.78$; $P=0.45$) (Fig. 4).

4. Discussion

Here we show that compared to a matched control group, patients with CBP rate moderately intense gustatory stimuli as significantly more intense. Three complimentary findings suggest that this reflects an increase in gustatory sensitivity rather than differences in hedonic processing of taste, rating

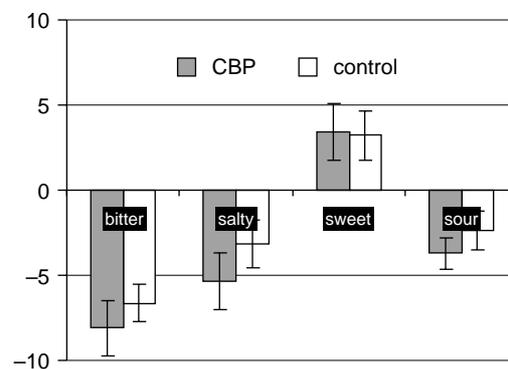


Fig. 3. Mean pleasantness/unpleasantness ratings for each of the four gustatory stimuli for the chronic back pain group (CBP) in gray and the control group in white. Error bars represent standard errors of the mean. No significant differences in ratings were observed between the CBP and control groups.

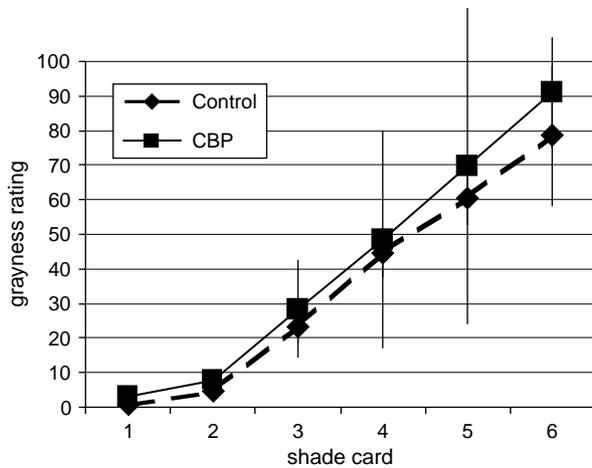


Fig. 4. Mean rating of the six gray cards ranging from white (1) to black (6). Error bars represent standard error of the mean. Data shown separately for control (solid line) and chronic back pain (CBP, disconnected line) subjects.

scale use, or a general tendency to react more strongly to sensory stimuli. First, the gustatory stimuli were rated as more intense but no more or less pleasant. Second, no differences were observed in the intensity ratings of the visual stimuli. Third, the CBP patients tended to have lower detection thresholds. This measure does not require a use of a rating scale and employs non-detectable or barely detectable stimuli. Hence, the only way to consistently make correct responses is to detect the taste. Therefore, while it is possible to respond purposefully to achieve a higher detection threshold, it is not possible to manipulate responses to achieve a lower threshold. Thus, even though this finding is only a trend it suggests that subjects did not knowingly manipulate responses.

The dissociation observed between the gustatory and visual modalities is in accordance with our hypothesis that the impairment of CBP patients (living with heightened pain for many years) generalizes to increased sensitivity to taste, which is co-localized with pain in the central nervous system. We show differences in taste between CBP patients and normal subjects after correcting for PROP responses. There is extensive literature showing that PROP sensitivity is related to lingual tactile acuity, and to density and diameter of fungiform papillae (Bartoshuk, 2000; Delwiche et al., 2001; Essick et al., 2003; Lucchina et al., 1998), but not related to bitter intensity of quinine (Delwiche et al., 2001), and not related to fat, saltiness, and sweetness perceptions (Yackinous and Guinard, 2001). Therefore, we can assert that the observed differences between CBP and controls are not due to differences in taste bud properties but rather to more central effects. The selectivity of the presence of CBP on taste, after matching for PROP, suggests specific interactions between the two brain networks: in primates, gustatory information is carried to the rostral division of the nucleus of the solitary tract. From here, second order fibers project to the parvocellular portion of the ventral posterior

medial nucleus of the thalamus (Beckstead et al., 1980), and most densely to the dorsal half of the anterior insula and adjacent operculum (Pritchard et al., 1986). A secondary projection exists in a region extending from areas 3a, 3b, 1, and 2 along the lateral margin of the precentral gyrus. Both regions are activated by peripheral stimulation of the gustatory nerves (Ogawa et al., 1984). Functional neuroimaging studies indicate that these same regions also respond to taste in the human brain, see (Faurion et al., 1999; Kinomura et al., 1994; O'Doherty et al., 2001; Small et al., 1999, 2003). Neurons that respond unimodally to taste stimulation have also been identified in the orbitofrontal cortex of the macaque (Kadohisa et al., 2005) and human brain (Small et al., 1999). Although not formally considered part of the gustatory system, the amygdala is highly interconnected with the classical cortical gustatory areas of the brain (Carmichael and Price, 1996; Mesulam and Mufson, 1982) and consistently responds to stimulation with taste (Frey and Petrides, 1999; O'Doherty et al., 2001; Small et al., 2003; Zald et al., 2002). The orbitofrontal taste region cortex appears to be relatively more sensitive to the pleasantness or unpleasantness of taste stimuli (Small et al., 2003; Zald et al., 2002).

All of the cortical regions involved in gustatory perception either receive or respond to nociceptive stimuli. In the thalamus the gustatory region is just adjacent to nociceptive regions, and electrical stimulation within this region evokes both pain and taste sensations in humans (Lenz et al., 1997). The exact relationship between gustatory and pain neurons in area 3a, 3b, 1 and 2 remains unknown, and electrical stimulation in and around the operculum rarely results in perception of taste (Van Buren, 1983). Here we highlight three brain regions, which appear critical to CBP and also to gustatory processing: (1) the anterior insula and (2) the medial prefrontal cortex (main brain regions activated during spontaneous fluctuations of pain of CBP, Baliki et al. Society for Neuroscience Abstract 2003) and (3) the thalamus (displays atrophy in CBP (Apkarian et al., 2004b)). The fact that the affective component of taste remains unchanged in CBP suggests that CBP pain and gustatory perception are represented separately within the medial prefrontal cortex. The insular cortex is the most frequently activated region of the brain in response to painful stimuli in human brain imaging studies (Apkarian et al., 2005; Derbyshire, 1999; Peyron et al., 2000), and electrical stimulation in posterior or mid-insula results in somatotopically-organized reports of pain (Ostrowsky et al., 2002). Activity in the anterior portion of insula increases with the number of years patients experience CBP. This is the same region that responds to taste. These findings suggest that the heightened sensitivity to taste observed in CBP may be related to hyperactivity of this region. It is possible that thalamic atrophy associated with CBP also leads to disinhibition in the gustatory areas. This may operate either through indirect influences of the thalamus upon the amygdala, or through direct interactions

within the thalamus, or through insular projections. Future human functional and morphometric brain imaging studies will be important in differentiating between these hypotheses and in determining the types of modulation chronic pain imposes on taste perception.

It is known that resection from the anterior medial temporal lobe including the amygdala in humans leads to increased taste intensity perception (Small et al., 2001a,b). The proposed explanation for this increase is that removal of amygdala modulation of taste regions leads to a release from inhibition. The site for this interaction is unknown. Pain perception has not been evaluated in this patient population, but the current results lead to the prediction that pain perception should also be increased.

Additionally, since olfactory inputs are also colocalized with taste in the insula (de Araujo et al., 2003; Scott and Plata-Salaman, 1999; Small et al., 2004) the present results predict that olfactory perception may also be heightened in CBP.

We attempted to match the patients and normal subjects with as many parameters as possible. Still, we cannot assert that there are no confounding factors that may influence the outcomes. At least life style and drug use are different between the groups. Extent of social interaction, mobility, and even food preferences may differ between the groups, and we have not documented these differences. Moreover, CBP patients certainly consume more drugs than normal subjects. We have not documented drug use in this specific CBP patient group. However, they are from a pool of CBP patients in which we have, in the past, quantified drug use (Apkarian et al., 2004b), where we observed that reliable information can be obtained in only about 50% of CBP patients, and in those cases, the main drugs consumed are NSAIDs, COX-2 inhibitors, and occasional consumption of opiates. This profile is very similar to a recent report of drug use in CBP (Vogt et al., 2005). Abnormal taste perception has been reported with different analgesics (Carr et al., 2004; Lucker et al., 1994), although there are no systematic studies on the subject, and reported effects are disruptions in taste. Generally, there is no evidence for antipyretics affecting taste, and even long term use of high or low doses of opiates seem to have minimal lasting effects on taste (Bogucka-Bonikowska et al., 2002; Stromberg et al., 1997). Therefore, even though we cannot rule out lifestyle and drug use confounds, their contribution is unlikely to be important especially since we observe increased sensitivity to taste in CBP.

In summary, the observed results provide a new approach with which the brain specificity of different chronic pain conditions may be dissected: if different chronic pain conditions impact the same brain circuitry then our results should generalize to other chronic pains, on the other hand if this abnormality is unique to back pain then it would imply the specific brain circuitry involved in back pain.

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