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ORBITOFRONTAL CORTEX: NEURONAL REPRESENTATION OF ORAL TEMPERATURE AND CAPSAICIN IN ADDITION TO TASTE AND TEXTURE

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Abstract—The primate orbitofrontal cortex is a site of convergence of information from primary taste, olfactory and somatosensory cortical areas. We describe the discovery of a population of single neurons in the macaque orbitofrontal cortex that responds to the temperature of a liquid in the mouth. The temperature stimuli consisted of water at 10 °C, 23 °C, 37 °C and 42 °C. Twenty-six of the 1149 neurons analyzed (2.3%) responded to oral temperature. The tuning profiles of the neurons to temperature showed that some of the neurons had graded responses to increasing temperature (27%), others responded to cold (10 °C) stimuli (27%), and others were tuned to temperature (46%). The neuronal responses were also measured to taste stimuli, viscosity stimuli (carboxymethyl-cellulose in the range 1–10,000 cP), and capsaicin (10 μM). Of 70 neurons with responses to any of these stimuli, 7.1% were unimodal temperature; 11.3% were temperature and taste-sensitive; 7.1% were temperature and viscosity-sensitive; and 11.3% were temperature, taste and viscosity sensitive. Capsaicin activated 15.7% of the population of responsive neurons tested. These results provide the first evidence of how the temperature of what is in the mouth is represented at the neuronal level in the orbitofrontal cortex and the first evidence for any primate cortical area that in some cases this information converges onto single neurons with inputs produced by other sensory properties of food, including taste and texture. The results provide a basis for understanding how particular combinations of oral temperature, taste, and texture can influence the palatability of foods.

Key words: food, temperature, palatability, orbitofrontal cortex, taste.

When we eat or drink, a taste sensation is elicited which may be accompanied by inputs from other modalities including the olfactory (the smell of food), and somatosensory ('mouth feel,' which can signal the presence of fat and other textures, and irritation), including thermosensory, modalities. The interaction between these inputs creates the sensation of flavour. The temperature of food and other substances in the mouth is important to their palatability (Zellner et al., 1988), with for example orange juice being usually more palatable when cold, and soup when hot. Although part of the effect of temperature on food palatability may be secondary to effects on texture, taste, and smell (Schiffman et al., 2000), the temperature itself may be important, and indeed, it is of interest to know the extent to which the temperature of food in the mouth is encoded separately from its taste, smell and texture. It is further likely that core temperature modulates the palatability of substances in the mouth at different temperatures, with for example a cold drink being more refreshing when the core temperature is high (Cabanac, 1971). In this investigation we discovered neurons in the orbitofrontal cortex, a brain region important in the palatability of food, that encode the temperature of what is in the mouth independently of taste, smell and texture. We also found that additional orbitofrontal cortex neurons respond to combinations of temperature with taste or texture inputs, helping to provide a basis for the particular palatability of foods with different sensory profiles. The results described here are new, in that there has been no previous investigation of the effects of oral temperature on the responses of orbitofrontal cortex neurons, a brain region implicated in responses to other sensory properties of foods (Rolls, 2000, 2004). Indeed, there has been no earlier investigation of the neuronal responses of any primate cortical area to oral temperature. Further, although oral temperature neuronal responses to water have been described in an insular cortical region in rats, no tuning profiles have been provided, and only three (Yamamoto et al., 1981, 1988), or two (Kosar and Schwartz, 1990a,b) temperatures were investigated.

In this paper we also investigated the effects of oral capsaicin, both because it is present in some palatable foods and produces oral sensations that can influence food palatability, but also because capsaicin affects VR1 receptors that are sensitive to temperatures of approximately 43 °C and above (Caterina et al., 1997, 1999; Patapoutian et al., 2003), and it was of interest to determine whether cortical neurons show systematic convergence between the effects of certain temperatures and the effects of capsaicin in the mouth.

In previous investigations of the sensory signals about the palatability of food that are important in the regulation of feeding in primates (see Rolls, 1995, 1997, 1999, 2000, 2004; Rolls and Scott, 2003), it has been shown that the primate orbitofrontal cortex (OFC) contains the secondary taste and olfactory cortex, and representations of the reward value of taste, smell, and flavor (Baylis et al., 1994; Rolls et al., 1989, 1990, 1996; Carmichael et al., 1994; Critchley and Rolls, 1996a; Rolls and Rolls, 1997; Rolls and Baylis, 1994). Somatosensory inputs reach the OFC

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Abbreviations: BJ, blackcurrant juice; CMC, carboxymethylcellulose; G, glucose; H, HCl; M, monosodium glutamate; N, NaCl; OFC, orbitofrontal cortex; Q, quinine HCl.

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(Carmichael and Price, 1995), and OFC neurons respond to astringent texture (Critchley and Rolls, 1996b). Rolls et al. (1999) discovered a neuronal representation in the macaque OFC of the texture of fat in the mouth. Rolls et al. (2003c) have also shown that there is a somatosensory input to the primate OFC which encodes the viscosity of what is in the mouth.

The aim of this study is to advance understanding of the representation of different types of sensory input in the OFC of the primate. Therefore we extended these previous investigations showing taste, olfactory, visual, and three somatosensory representations (fat texture, astringency and viscosity) in the OFC to temperature, which is an important oral sensory input for the reasons set out above, and to capsaicin.

EXPERIMENTAL PROCEDURES

Subjects

The recordings were made in three hemispheres of two rhesus macaques (*Macaca mulatta*; one female weighing 2.6–3.3 kg and one male weighing 5.1–5.6 kg; 38 neurons were from the female, and 32 from the male, and the neuronal populations were similar in the two monkeys). The monkeys were pair housed in foraging home cages. To ensure that the macaques were willing to ingest the test foods and fluids during the recording sessions, they were on mild food (150 g of nutritionally balanced mash plus fruits, boiled chicken eggs, nuts and seeds) and fluid (1 h/day *ad libitum* water) deprivation, in that both were provided after the daily recording session. The monkeys showed steady increases in body weight. All procedures, including preparative and subsequent ones, were carried out in accordance with the "Policy on the use of animals in neuroscience research" of the Society for Neuroscience, and were licensed under the U.K. Animals (Scientific Procedures) Act 1986. The procedures minimized the number of animals (2) involved in the study and optimized their welfare including for example the provision of group housing and environmental enrichments.

Recordings

Recordings were made from single neurons in the OFC, which included areas in which taste and olfactory responses have previously been described (see Rolls and Baylis, 1994; Rolls, 1997), using neurophysiological methods as described previously (Rolls et al., 1990; Scott et al., 1986a,b). The recordings were made with epoxylite-coated single neuron tungsten microelectrodes (Frederic Haer & Co., St. Bowdoinham, ME, USA; unzapped, 5–10 MΩ at 1 kHz). After several tracks when the impedance had fallen below 2 MΩ, we recoated the electrodes with epoxylite (6001M; Epoxylite Ltd., Bradford, UK) resulting in 5–10 MΩ impedance and good isolation (Verhagen et al., 2003a). The signal-to-noise ratio was typically 3:1 or higher.

For on-line monitoring of neural activity and for determining the randomized permutation stimulus sequence during an experiment a computer (Pentium) with real-time digital and analog data acquisition collected spike arrival times and displayed a peristimulus time histogram and rastergrams, and displayed the number spikes in 1 and 3 s post-stimulus periods. The spikes for this system were derived from an oscilloscope Schmitt trigger set to trigger on spikes in the signal from the microelectrode after amplification and band-pass filtering (500–5000 Hz). To ensure that the recordings were made from single cells, the interspike interval was continuously monitored to make sure that intervals of less than 2 ms were not seen, and the waveform of the recorded action potentials was continuously monitored. The data were also collected using a Datawave Discovery Inc (Tucson, AZ, USA) system which digitised the signal (12 bit, 16 kHz) for 8 s after stimulus onset. The spikes were sorted off-line using the cluster cutting method provided with the Datawave system. This procedure was straightforward as the data were collected with single neuron microelectrodes which typically recorded from only one neuron at a time with a good signal-to-noise ratio ($>$3:1). The inset at the bottom right of Fig. 1 shows the good isolation of the spikes of a single neuron achieved by virtue of the high impedance single neuron recording microelectrodes and the cluster cutting. In all cases, apart from 5, the neurons described here were recorded at separate recording sites. The recording sessions lasted 4 to 6 h and were conducted daily. To prevent visual associative input from evoking neural activity, we prevented the monkeys from seeing the stimuli by a view-obstructing screen. For further details see Rolls et al. (1990). No more than two complete experiments, on different neurons, were performed per day to limit the effects of satiety on neural responses. (The total application volume was 70 ml for the complete set of replications of the full stimulus set including rinses.) Although satiety was not being investigated in this study, we wished the monkeys to be willing to accept the food-related stimuli, as we have shown that neuronal responses in the OFC to the taste, smell, and sight of food become diminished when the monkey becomes satiated (Rolls et al., 1989; Critchley and Rolls, 1996a). We did check at the end of recording sessions that the monkey was still willing to accept the food-related stimuli.

Localization of recordings

X-radiography was used to determine the position of the microelectrode on every recording track relative to permanent reference electrodes and to the anterior sphenoidal process. This is a bony landmark whose position is relatively invariant with respect to deep brain structures (Aggleton and Passingham, 1981). On each track, one X-ray in the coronal plane, and one in the sagittal plane, was taken. Microlesions made through the tip of the recording electrode during the final tracks were used to mark the location of typical units. These microlesions together with the associated X-radiographs allowed the position of all cells to be reconstructed in the 50 μm brain sections with the methods described by Feigenbaum and Rolls (1991).

Stimuli

OFC neurons were tested for their responsiveness to the set of temperature stimuli shown in Table 1, and also to provide evidence on other stimuli to which the neurons might be tuned, to the taste and viscosity stimuli (at room temperature) shown in Table 1. The temperature series was provided by water at T10 °C (chosen as the cold stimulus; commercial cold drinks are served at 6 °C), at T42 °C (warm/hot but not noxious), T37 °C (body temperature), and T23 °C (room temperature). These temperature stimuli were produced by keeping the 10 ml applicator pipettes (described under stimulus delivery) in a 100 ml bottle containing the same water as that inside the applicator pipette, with the bottle itself maintained in a separate water bath controlled at T10 °C, T37 °C, T42 °C, and T23 °C (room temperature). As the temperature stimulus was delivered directly from the applicator to the mouth, there was no effect of the heat capacity of the applicator on the temperature of the water delivered to the mouth.

The gustatory stimuli used included 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M quinine HCl (Q), and 0.1 M monosodium glutamate (M). The concentrations of most of the taste stimulus were chosen because of their comparability with our previous studies, and because they are in a sensitive part of the dose-response curve. (Concentration-firing rate response functions for single neurons in the primate nucleus of the solitary tract to G, N, H and QHCl are shown by Scott et al., 1986a; and in the

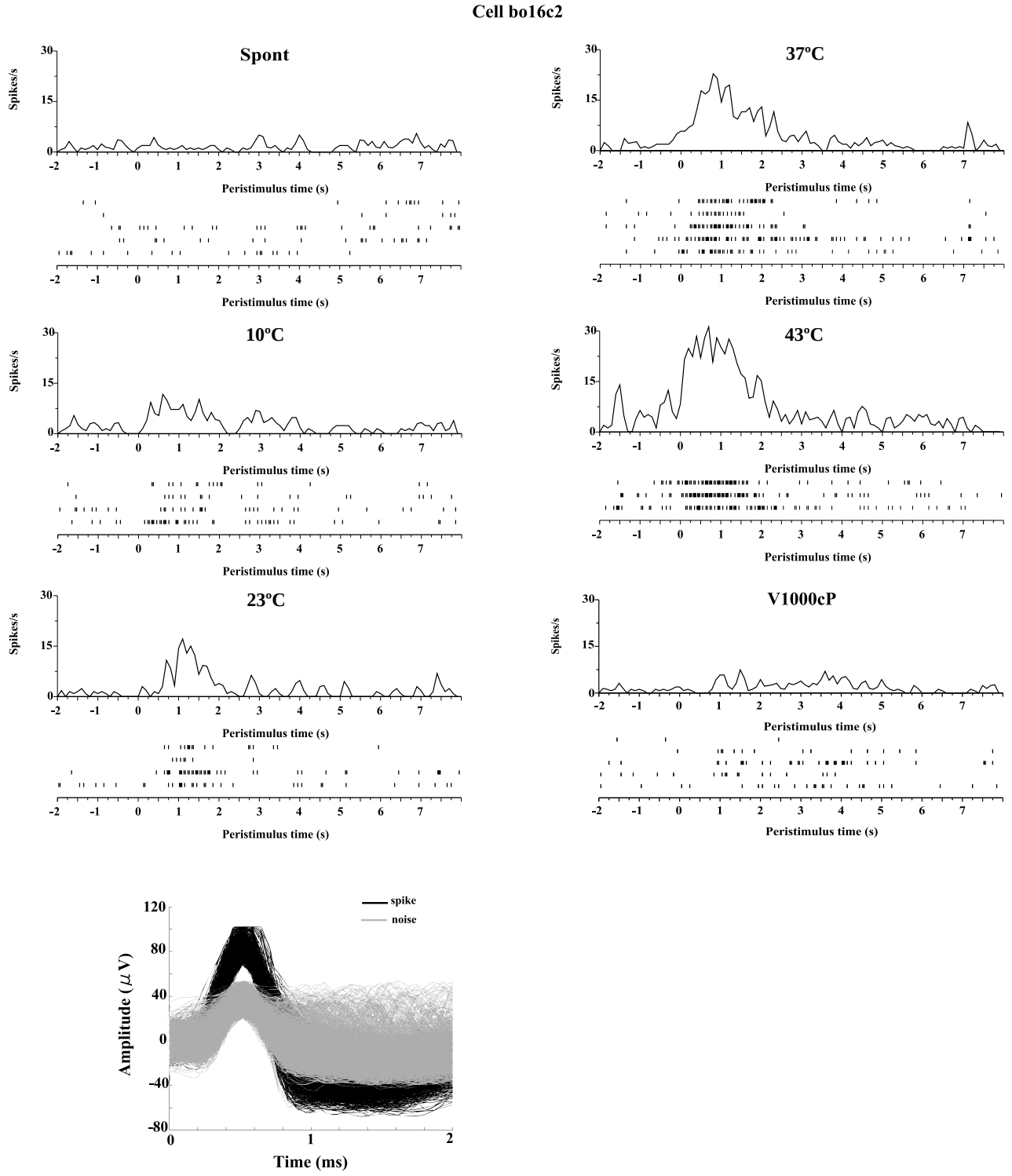

Fig. 1. Peri-stimulus-time histograms and rastergrams of a temperature responsive neuron (bo16c2) for the different oral temperature stimuli tested. The stimulus was delivered at time 0. This neuron's firing rate increased with increasing temperature. The inset at the bottom right shows 407 spikes of this single neuron, together with 2872 other noise traces, to indicate that the signal to noise ratio allowed perfect separation of the spikes of the single neuron being recorded from the noise.

insula by Scott et al., 1991; further, for each tastant the concentration we used was approximately 10 times the concentration at which these neurons started to respond, except for G, for which a higher concentration was used so that the same solution could be used in satiety experiments, see e.g. Rolls et al., 1989). Distilled water at T23 °C was useful as one temperature series, but the same stimulus was of interest in relation to the other taste stimuli (which were delivered at 23 °C), and to the viscosity stimuli, in that

Table 1. Stimuli

Stimulus	Abbreviation	Concentration	MW	Temperature (°C)	Viscosity (cP)	Chemical group
Glucose	G	1 M	180	23	1	Monosaccharide aldohexose
Blackcurrent	BJ	20%		23	1	Mixture
Monosodium glutamate	M	0.1 M	187	23	1	Amino acid salt
NaCl	N	0.1 M	58	23	1	Inorganic salt
HCL	H	0.01 M	36	23	1	Inorganic acid
Quinine HCL	Q	0.001 M	387	23	1	Alkaloid
Water	T10 °C			10	1	
Water	T23 °C/V1cP			23	1	
Water	T37 °C			37	1	
Water	T42 °C			42	1	
CMC	V10cP	0.2 g+11 V1	700,000	23	10	Polysaccharide
CMC	V100cP	4.0 g+11 V1	700,000	23	100	Polysaccharide
CMC	V1000cP	11.0 g+11 V1	700,000	23	1000	Polysaccharide
CMC	V10,000cP	24.0 g+11 V1	700,000	23	10,000	Polysaccharide
Capsaicin	Cap	10 μM		23	1	Vanillyl amide

the viscosity of the water was approximately 1 cP (and is also termed V1cP in Table 1). For an additional comparison, the neuronal responses were tested to 20% blackcurrant juice (BJ; Ribena, GlaxoSmithKline, Middlesex, UK), because with its complex taste and olfactory components and high palatability it is an effective stimulus when searching for and analyzing the responses of cortical neurons (Rolls et al., 1990).

A viscosity series was made with carboxymethylcellulose (CMC; Sigma; high viscosity, Mw 700,000), an odorless and tasteless thickening agent used widely in the food industry (with psychophysics that supports this reported by Rolls et al., 2003c). The apparent viscosity was assessed using a calibrated Brookfield rotary viscometer (type LVT; Brookfield Engineering Laboratories Inc., Middleboro, MA, USA) at 60 r.p.m. (shear rate approximately 12 s^{-1}) at 23 °C. (The term apparent viscosity is used to indicate that the CMC solutions do not behave rheologically as Newtonian fluids: they show shear-thinning behavior. Further details of the viscosity stimuli are provided by Rolls et al., 2003c.) Concentrations (in g CMC added to 500 ml water) yielding 1, 10, 100, 1000 and 10,000 cP (V1, V10, V100, V1000 and V10,000; reliability±10%) solutions were: 0.0, 0.1, 2.0, 5.5 and 12.0 g CMC, respectively. The solutions were mixed until they were optically clear. Viscosity was assessed at room temperature after air bubbles had disappeared. (Note that 1 cP=1 mPascal s. For those not familiar with viscosity values, it may be helpful to note that the viscosity of water at 20 °C is approximately 1 cP, of the corn oil used for cooking is typically 50–60 cP, and of treacle, known in the U.S. as blackstrap molasses, is typically 5000–10,000 cP. The perceived thickness of a viscosity series increases approximately linearly with the logarithm of the viscosity; see Theunissen and Kroeze, 1995; Christensen, 1979.)

Capsaicin was used as an additional stimulus, made up as a 10 μM solution containing 0.3% ethanol (Cap). The background to use of this stimulus is that capsaicin can activate the TRPV1 (i.e.VR1) vanilloid receptor which can also be activated by stimuli close to the level of our hot (T42 °C) stimulus (Caterina et al., 1997). We note that capsaicin is perceived to have a bitter taste (Green and Schullery, 2003).

The stimuli were kept in the dark at −20 °C for up to 1 month. After thawing they were used for up to 5 days stored overnight at 4 °C in the dark.

Stimulus delivery

The general method for stimulus delivery and accurate stimulus onset marking (Rolls et al., 1990) was modified by introducing repeater pipettes (Verhagen et al., 2003b). We used repeater pipettes (Eppendorf AG, Hamburg, Germany; type Multipette Plus), and pipette tips (Combitips Plus; 10 ml), which were modified by insertion of a stainless steel wire (0.5 mm diameter) into the lumen 10 mm from the tip. The wire was tightly coiled approximately 10 times around the tip extending toward the neck, and glued at the neck with epoxy glue. For stimulus delivery, the pipette tip and thus the wire which encircled it (and was connected electrically to the fluid inside the pipette) was placed on antistatic conducting foam, which was in turn connected to an impedance-sensitive device which could send a Schmitt-triggered pulse to the data acquisition system. When fluid was expelled from the pipette held just inside the lips and touched the tongue, the impedance to ground changed, and the pulse was triggered. We placed 10 mm-long cones cut from 200 μl Gilson pipette tips onto the tip of the repeater pipette tip, creating a fluid-free lumen, in order to prevent the system from being triggered when the tip touched the monkey's lips. For reliable triggering, a concentration of 5 mM N to make the solution sufficiently conductive for the impedance system to trigger was used. (This concentration is well below the salivary N+KCl concentration of approximately 25–30 mM (Nagler and Nagler, 2001; Guinard et al., 1998; Morino and Langford, 1978; Bartoshuk, 1974). All water soluble stimuli were thus made up to contain 5 mM N. The tips were wiped clean before each stimulus presentation. To allow for consistent flow patterns, air bubbles in the pipette were removed and the pipette tips were cut back to an opening diameter of 1.5 mm. For chronic recording in monkeys, a manual method for stimulus delivery is used because it allows for repeated stimulation of a large receptive surface despite different mouth and tongue positions adopted by the monkeys (Scott et al., 1986a,b). The stimulus application volume was 200±10 μl, because this is sufficient to produce large gustatory neuronal responses which are consistent from trial to trial, and yet which do not result in large volumes of fluid being ingested which might, by producing satiety, influence the neuronal responses (Rolls et al., 1989, 1990). The monkey for all stimuli used the tongue to move the liquid administered through the mouth until the first bolus was swallowed after 2–3 s.

The monkey's mouth was rinsed with 200 μl T23 °C water during the inter-trial interval (which lasted at least 30 s, or until neuronal activity returned to baseline levels) between taste stimuli. The complete stimulus array was delivered in random sequence. (Four 200 μl-rinses with T23 °C were given after capsaicin, allowing the subjects to swallow after each rinse.) All the stimuli shown in Table 1 were delivered in permuted sequences,

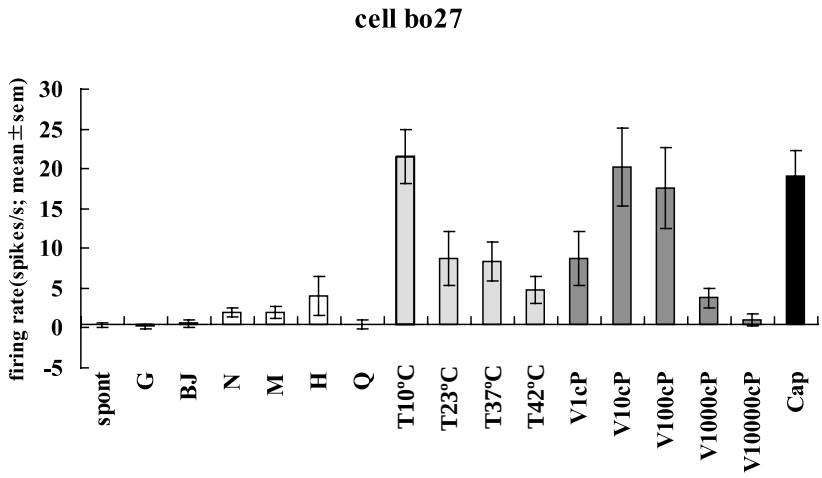

Fig. 2. Responses of primate OFC neuron (bo27) to temperature, taste, viscosity, and to capsaicin. The mean and the standard error of the mean responses calculated in a 1 s period over four to six trials are shown here and elsewhere unless otherwise indicated. The spontaneous (spont) firing rate is shown. The stimuli were 1 M G, 0.1 M N, 0.1 M M, 0.01 M H and 0.001 M Q, fruit juice (BJ), the temperature series (T10 °C, T23 °C, T37 °C and T42 °C), the viscosity series (V1cP, V10cP, V100cP, V1000cP and V10,000cP) and capsaicin (Cap).

with the computer specifying the next stimulus to be used by the experimenter. The spontaneous firing rate of the neuron was estimated from trials in which no stimulus delivery occurred.

Data analysis

After cluster cutting of the spikes with Datawave software, the numbers of spikes of the single neuron in 80 time bins each 100 ms long starting at the onset of the stimulus were obtained using SPSS (SPSS Inc., Chicago, IL, USA). Statistical analysis was performed on the numbers of spikes in the first 1 s period after stimulus onset, which was sufficiently long to include firing to even viscous liquids, and sufficiently short so that low viscosity taste stimuli were still activating the neurons, as shown in Fig. 2 of Rolls et al., 2003c. An ANOVA was performed (with SPSS, and with four to eight trials for each stimulus) to determine whether the neuron had significantly different responses to the set of stimuli, and if so, post hoc Tukey's tests were performed to test for significant differences between individual stimuli. If the main ANOVA was significant, three further ANOVAs were performed to test for differences in neuronal responses between the set of taste stimuli (G, N, H, Q, M and T23 °C), between the members of the temperature T10 °C–T42 °C, and between the members of the viscosity V1cP–V10,000cP series. Systat 10 (Systat Software Inc., Point Richmond, CA, USA) was used for the generation of Pearson product-moment correlation coefficients calculated between the stimuli using the responses of all the neurons analyzed, and graphical presentation of stimulus similarity using multi dimensional scaling (loss function: Kruskal; regression: mono) and cluster analysis (linkage: average, distance: Pearson). (Multidimensional scaling produces a space based in this case on the correlations between the responses to the different stimuli of the population of 26 neurons in which the distances in the space between the stimuli reflects the correlation between them [Schiffman et al., 1981; Scott et al., 1986a]. Cluster analysis is also based on the inter-stimulus correlation matrix, and can be used to produce a dendrogram showing how similar, and how different, the clusters are from each other [Scott et al., 1986a].)

A taste cell was defined by a significant effect in the ANOVA performed across the stimulus subset (T23 °C, G, N, M, H and Q) on the number of spikes during the first second after stimulus onset. Similarly, the criterion for being sensitive to temperature was based on a significant effect in the ANOVA between the set of stimuli T10 °C–T42 °C. The criterion for being sensitive to viscosity was based on a significant effect in the ANOVA between the set of stimuli V1cP–V10,000cP. The critical α level was set at $P<0.05$ (although for most cells 54/70, the P value in the overall ANOVA was <0.001). The test for capsaicin sensitivity was a two-tailed *t*-test comparing the responses of the neuron to capsaicin and to T23 °C water.

A Fisher (1932) probability combination (or generalized significance or exact probability) test was performed to check that the statistically significant results in the orally responsive cells could not reflect just chance statistical results. (By chance, if for example one statistical test was performed on 100 cells, then five of the tests might be expected to be significant at $P<0.05$.) The Fisher combination test calculates the exact probability of obtaining a set of significance values by chance in independent tests. The procedure calculates $-2\ \Sigma \ln p_i$, which has a χ^2 distribution with $2n$ degrees of freedom, and the sum is over the n probability values p_i obtained in separate tests. This measure is well established and asymptotically Bahadur optimal (Littell and Folks, 1971; Zaykin et al., 2002).

The breadth of tuning metric of Smith and Travers (1979) was calculated as follows. The proportion of a neuron's total response that is devoted to each of the four basic stimuli can be used to calculate its coefficient of entropy (H). The measure of entropy is derived from information theory, and is calculated as

$$H = -k \sum_i p_i \log p_i$$

where H=breadth of responsiveness, k=scaling constant (set so that $H=1.0$ when the neuron responds equally well to all stimuli in the set of size n), p_i=the response to stimulus i expressed as a proportion of the total response to all the n stimuli in the set. The coefficient ranges from 0.0, representing total specificity to one of the stimuli, to 1.0, which indicates an equal response to all of the stimuli. The sparseness of the representation a can be measured (Rolls and Treves, 1998; Rolls and Deco, 2002; Rolls and Tovee, 1995), by extending the binary notion of the proportion of neurons that are firing, as

$$a = \left(\sum_{i=1,N} r_i/N \right)^2 \Big/ \sum_{i=1,N} (r_i^2/N)$$

where r_i is the firing rate of the ith neuron in the set of N neurons. The sparseness is within the range 0–1, and assumes the value 0.5 for a fully distributed representation with binary encoding; and

1/*N* for a local or grandmother cell representation with binary encoding. These measures of the fineness of the tuning of neurons are important in understanding the neuronal encoding of information (Rolls and Treves, 1998; Rolls and Deco, 2002).

Screening cells

While searching for neurons, we continuously applied samples from our stimulus set: G, N, Q, BJ, T10 °C, T23 °C, T42 °C, V10cP and V100cP. We also tested for visual responsiveness (to the sight of food, a saline associated square plaque, the approach of a taste stimulus toward the mouth, objects, faces, head movement, and lip-smacking) and auditory responsiveness (a 500 Hz tone, coo-calls, grunts and vocalization) as stimuli of these types do activate some OFC neurons (Rolls et al., 1996). When neurons were insensitive to these stimuli, we classified them as non-responsive. Only cells responding consistently to at least one stimulus of the array were recorded, all stimuli being applied four to six times in permuted sequences.

RESULTS

The data described in this paper were obtained during recording tracks in three hemispheres of two monkeys. Out of 1149 neurons analyzed in the OFC region, 70 neurons (6.1%) responded to temperature, taste, viscosity, capsaicin, and/or fat texture. The responses of these 70 neurons were typically (in 54/70 cases) extremely significant ($P<0.001$; see Experimental Procedures). To confirm that the significant responses of this population of 70 neurons could not have arisen by chance, we performed a Fisher (1932; see Experimental Procedures) probability combination test across the population of 1149 neurons, and found a χ^2 value of 3636 ($df=2298$), which corresponds to a z value of 17.5, $P \ll 10^{-16}$. Thus the responses of the 70 neurons to taste, viscosity etc. (across all 25 stimuli) were very unlikely to be due to chance. We further checked that the 26 neurons with significant ANOVAs between the four different temperature stimuli were unlikely to be related to chance, and found with a Fisher exact probability test a χ^2 value of 2077 ($df=70$), which corresponds to a z value of 47.8, $P \ll 10^{-16}$. Thus the responses of the 26 neurons to temperature were very unlikely to be due to chance. Visual responses (objects, movement) were clear in 14.4%, and 0.6% showed auditory responses. The remainder of the neurons (78%) was unresponsive to the stimuli used.

The responses of a temperature-responsive neuron (bo16c2) are illustrated in Fig. 1 with a peri-stimulus time histogram (psth) and rastergrams shown for each of the temperature conditions, run originally in random order. This neuron showed a graded increase in its firing as the temperature increased. The responses to the different members of the temperature series calculated over the first 1 s post-stimulus period (which, as shown in Fig. 1 is when the neurons recorded in this investigation responded to the temperature stimuli) were significantly different from each other ($F[3,14]=6.2$, $P=0.007$), allowing us to classify it as a temperature-responsive (i.e. discriminating) neuron. (This neuron was also taste-responsive, with the best taste stimulus, G, producing a firing rate similar to that produced by T42 °C.) As noted in the methods the monkey swallowed the first bolus of the liquid within 2–3 s of its administration, but no phasic activity related to mouth movements or swallowing is evident in Fig. 1, or was found in any of the OFC neurons described here. To document this, rastergrams and a peristimulus time histogram is included in Fig. 1 for the stimulus cellulose V1000 cP, which induced several tongue and mouth movements, but no neuronal activity was phasically related to this. Moreover, none of the 70 neurons with responses to oral stimuli responded when in a pre-screening test, mouth and tongue movements were made to the sight of an approaching syringe containing food.

Fig. 2 shows another example of an oral thermosensitive neuron (bo27). This cell responded differently to different temperature stimuli ($F[3,15]=9.4$, $P=0.001$), and was a cold-responsive neuron in that its main response within the temperature series was to the 10 °C stimulus. (This was supported by the post hoc tests, which showed that the response to T10 °C was significantly different to the responses to all the other stimuli in the temperature set, which were not different to each other.) This neuron

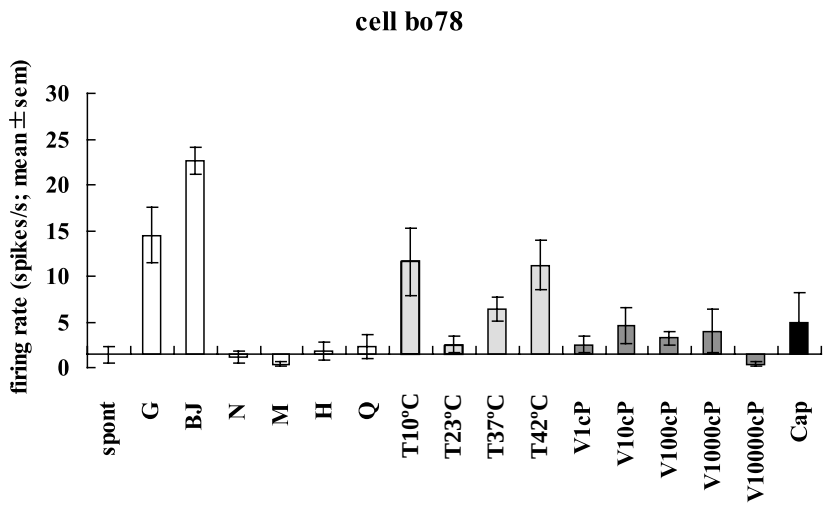

Fig. 3. Responses of primate OFC neuron (bo78) to temperature and to taste. Conventions as in Fig. 2.

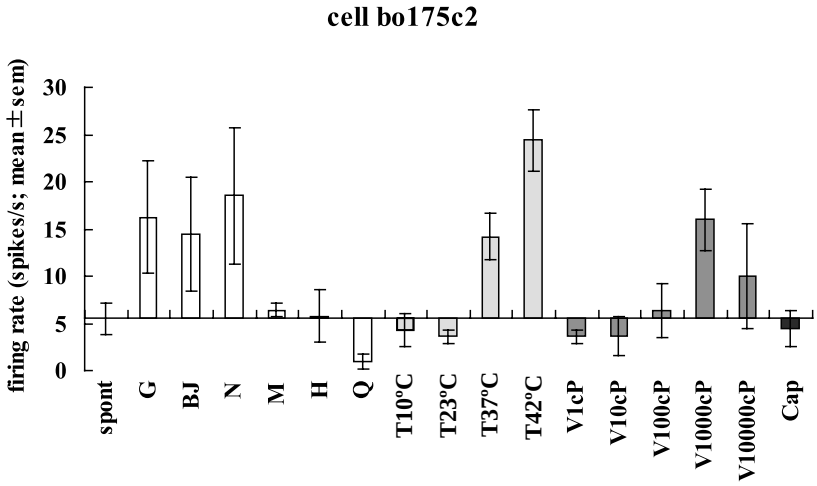

Fig. 4. Responses of primate OFC neuron (bo175c2) to temperature, taste, and to viscosity. Conventions as in Fig. 2.

also discriminated between the viscosity stimuli (as shown by the one-way ANOVA performed on the set of viscosity stimuli, F[4,19]=7.3, P=0.001). Within the viscosity series, the largest responses were to V10cP and V100cP. The neuron did not respond to the taste stimuli. The neuron also responded to capsaicin (P<0.05, compared with T23 °C, i.e. water), and this was of interest in that this was a cold-responsive and not a warm-responsive neuron. These results thus show that this neuron had thermal and somatosensory but not taste responses.

Fig. 3 shows another neuron (bo78) which had responses to temperature (F[3,17]=4.68, P=0.015), with tuning to temperature stimuli, in that there was no response to T23 °C, and the largest responses were to T10 °C and T42 °C. The neuron was bimodal, with responses that discriminated between the taste stimuli (F[5,26]=14.45, P<0.001), and its best responses to G and BJ. This neuron did not respond to the viscosity series or to capsaicin.

Fig. 4 shows a trimodal neuron (bo175c2) which had responses to temperature (F[3,15]=22.95, P<0.001), with a good response to T37 °C and its best response within the temperature stimulus set to T42 °C. The taste responsiveness (F[5,20]=4.75, P=0.005) was to G and N but not to M, H and Q. The viscosity responsiveness (F[4,17]=4.06, P=0.017) was tuned to V1000cP. Although this neuron responded to warm/hot (T42 °C) best, there was not response to capsaicin. The neurons illustrated in Figs. 3 (bo78) and 4 (bo175c2) show that there was not special relation between responsiveness to particular temperatures and particular tastes (see further, Discussion).

Fig. 5 shows the sensory inputs that influenced the neurons. Of the 70 neurons in the sample with responses to any of the stimuli, 28 (40%) neurons were unimodal (20 unimodal taste, five unimodal temperature, and three unimodal viscosity neurons), 21 (30%) neurons were bimodal (eight bimodal taste and temperature, five bimodal temperature and viscosity, eight bimodal viscosity and taste neurons), and eight (11%) neurons were multimodal with responses to taste, temperature and viscosity (see Fig. 5). (Other neurons responded for example to fat texture; see Verhagen et al., 2003b.) The findings provide clear evidence for convergence of taste and somatosensory (thermosensitive and/or texture-sensitive) inputs onto some neurons in the OFC (see Figs. 3 and 4), and also that each type of input is represented independently of the others.

Single neuron recording provides excellent evidence about the form of the representation provided in a given brain area. We provide this evidence (without any averaging together of the responses of different neurons) in Fig. 6, which shows the temperature profiles of each of the 26 thermosensitive neurons. All of the neurons shown had a significant ANOVA performed across the set of four temperature stimuli. The neurons can be classified for the purposes of arrangement in Fig. 6 using hierarchical cluster analysis based on the responses within the temperature series, with the following groups: Warm Linear (n=8: A–H), Cold Increasing (n=7: I–O), Inverted tuned (n=6: P–U), Inverted tuned (n=3: V–X), and neurons Y and Z which were clustered separately. In terms of the temperature stimulus to which the 26 neurons had the largest change from spontaneous rate, 13 (50%) had their best responses to T10 °C, two (8%) had their best responses to

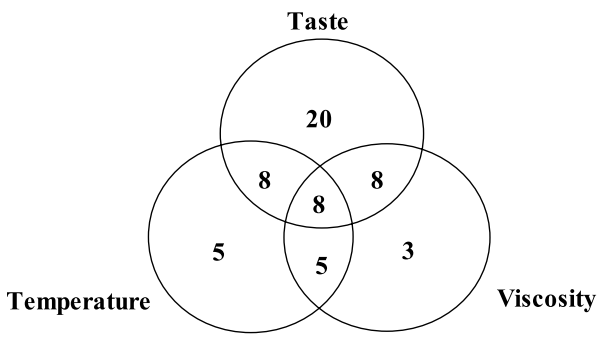

Fig. 5. A Venn diagram indicating the number of neurons sensitive to each modality as defined in the methods section.

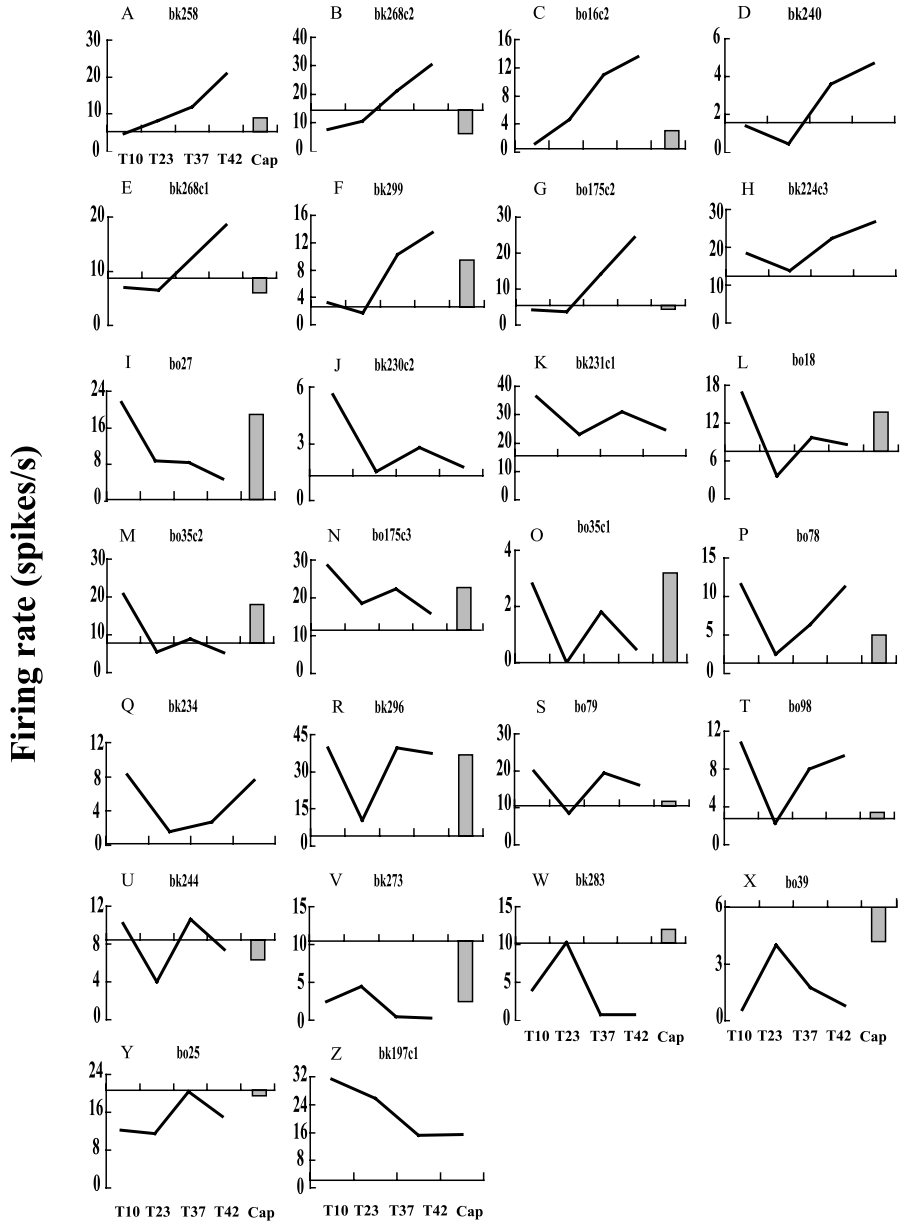

Fig. 6. Mean response profiles. Twenty-six thermosensitive neurons were classified into six groups.

T23 °C, two (8%) had their best responses to T37 °C, and nine (34%) had their best responses to T42 °C. The breadth-of-tuning metric (Smith and Travers, 1979) to H, Q, N and G of these 26 thermosensitive neurons was 0.85±0.03 (mean±S.E.M.), and to T10 °C, T23 °C, T37 °C and T42 °C 0.88±0.02. The corresponding sparsenesses (as defined by Rolls and Deco 2002 and used by Rolls et al., 2003c) are 0.73±0.04 and 0.77±0.03. The responses of these neurons to capsaicin are also shown in Fig. 6. Of the temperature-sensitive neurons with significant differences in their firing to capsaicin and its solvent T23 °C water (bk299, bk296, bo25, bo18 and bo27), two had similar responses to warm (T42 °C), and two had similar responses to cold (T10 °C). Thus there was no consistent tendency of the neurons that responded in some way to both capsaicin and temperature to respond to warm (T42 °C) stimuli. Moreover, of the nine neurons with responses to warm stimuli, only two responded to capsaicin. Conversely, of the eight neurons that responded to capsaicin, only two responded to warm (T42 °C) stimuli, and two responded to cold (T10 °C) stimuli.

We examined whether there were differences of the temperature responsiveness of neurons with and without taste inputs. There were no significant differences in the mean temperature profiles of the neurons without and with taste inputs (though the response in spikes/s to temperature was on average larger for the neurons that did not have taste inputs, 15.0 vs 9.0 spikes/s, $P<0.002$). Similarly, there was

Table 2. Correlations between the stimuli based on the responses of the population of oral thermosensitive neurons

	G	BJ	N	M	H	Q	T10	T23/V1	T37	T42	V10	V100	V1000	V10,000	Cap
G	1.00														
BJ	0.81	1.00													
N	0.14	0.26	1.00												
M	−0.01	0.14	0.83	1.00											
H	0.13	0.35	0.70	0.91	1.00										
Q	0.07	0.29	0.74	0.91	0.90	1.00									
T10	0.13	0.43	0.45	0.61	0.80	0.74	1.00								
T23/V1	0.22	0.35	0.71	0.69	0.65	0.77	0.73	1.00							
T37	0.42	0.60	0.60	0.70	0.82	0.74	0.76	0.64	1.00						
T42	0.66	0.71	0.58	0.50	0.60	0.50	0.50	0.47	0.89	1.00					
V10	0.29	0.43	0.53	0.54	0.59	0.63	0.69	0.73	0.77	0.67	1.00				
V100	0.22	0.43	0.61	0.67	0.77	0.73	0.81	0.73	0.89	0.73	0.91	1.00			
V1000	0.42	0.52	0.63	0.60	0.64	0.56	0.56	0.62	0.82	0.78	0.74	0.84	1.00		
V10,000	0.31	0.41	0.53	0.62	0.62	0.57	0.48	0.64	0.72	0.60	0.62	0.71	0.87	1.00	
Cap	−0.08	0.16	0.37	0.69	0.85	0.75	0.89	0.64	0.72	0.41	0.63	0.78	0.55	0.60	1.00

no difference in the mean profile of responsiveness to the taste stimuli of neurons without and with temperature inputs. (This result was confirmed by a two-way ANOVA, interaction term $F(3,92)=0.52$, ns.) These results indicate that the temperature-responsive neurons with and without taste inputs were not differently tuned to temperature, and vice versa.

To examine the similarities and differences between the stimuli that were represented by the population of neurons, hierarchical cluster analysis and multidimensional scaling (based on the correlations between the stimuli as encoded by the population of 26 temperature-responsive neurons, as shown in Table 2) was performed (Figs. 7 and 8). This analysis was based on the first 1 s of post-stimulus activity. In the dendrogram (Fig. 7) the T37 °C and T42 °C were relatively close but well separated from the other temperature stimuli. Indeed, the level at which representations of the different temperatures were joined in the dendrogram was 0.62 (see Fig. 7), indicating that the neurons as a population discriminated well between the different temperature stimuli. Interestingly, capsaicin was not close to the high temperature (T42 °C). The dendrogram also shows that this population of oral thermosensitive neurons in the primate OFC also responds as a population differently to different tastes, and has some differences in its responsiveness to different oral viscosities (see Fig. 7).

The multidimensional scaling analysis in Fig. 8 based on the responses of the 26 oral thermosensitive neurons shows that this population of neurons separates the re-

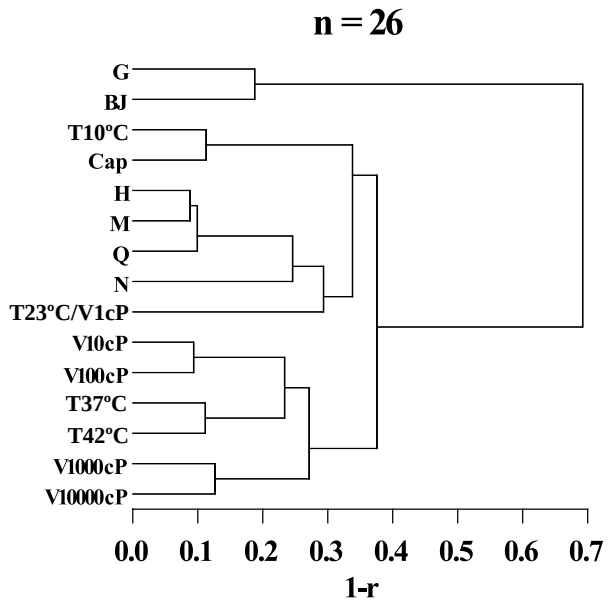

Fig. 7. A stimulus dendrogram based on the 26 thermosensitive neurons tested in the study. (1-r) is the measure of dissimilarity between the responses of the population of neurons to the different stimuli (*r* is the Pearson correlation coefficient).

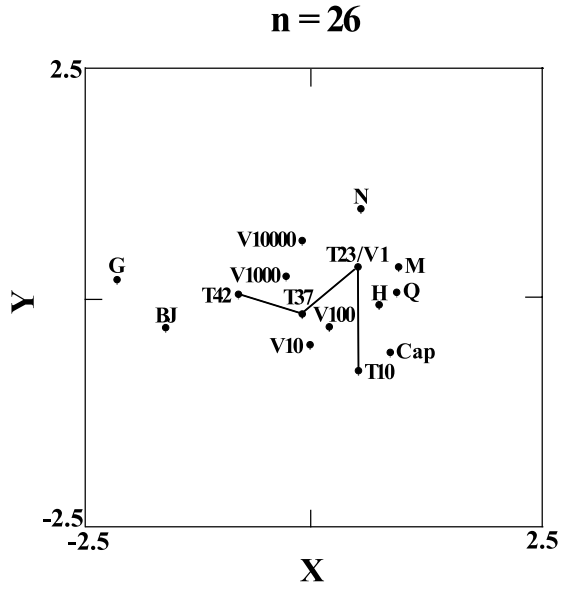

Fig. 8. A stimulus space (multidimensional scaling) of the stimulus similarity based on 26 thermosensitive neurons in the study. For stimulus abbreviations see Table 1. The distances between two stimuli in this space reflect the distances between the representations of the two stimuli by the population of 26 thermosensitive neurons as measured by multidimensional scaling.

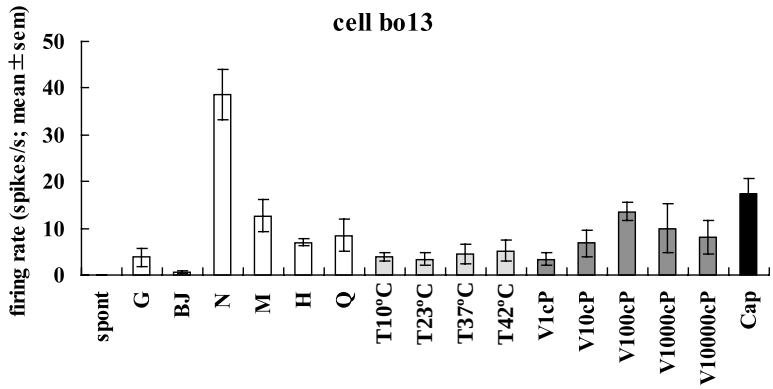

Fig. 9. Firing rates (mean±S.E.M.) of neuron bo13 which responded to the capsaicin and taste.

sponses to different temperatures well, in that the different temperatures are well spread out in the MDS space. (The temperature stimuli are highlighted by being joined by lines.) Corresponding, the separated positions of the taste stimuli in the space, show that this population of oral thermosensitive neurons responds differently to different tastes. In addition, the viscosity stimuli are reasonably separated in this MDS space, on the second or y dimension. (Two dimensions accounted for 94% of the variance.) It is notable that for each stimulus type is a generally continuous representation as one moves across parts of the space, consistent with efficient encoding of the quantitative point in the space by neuronal population encoding.

The cluster and MDS analyses shown in Figs. 7 and 8 are based on the correlations shown in Table 2, which of course reflect the average correlation between the stimuli as reflected by the whole population of neurons. Individual neurons had much lower correlations between their responses to pairs of stimuli. For example, although the correlation between the responses to T10 °C and T23 °C of the population of thermosensitive neurons was 0.73, the difference in firing rate to these two stimuli of for example the neuron shown in Fig. 3 was highly statistically significantly different (post hoc Tukey $P<0.008$). Thus the average correlations across the population of neurons in their responses to pairs of stimuli shown in Table 2 and reflected in Figs. 7 and 8 should not be taken to detract from the fact that individual neurons, and thus the population as a whole, were able to discriminate between all of the stimuli very significantly. (We checked that the cluster and MDS analyses themselves were robust with this number of neurons by repeating the analyses with different sets of five neurons removed from the analysis. The cluster and MDS analyses were robust to this procedure, showing that there were sufficient neurons in these population analyses.)

Of the 51 neurons tested with capsaicin, eight neurons responded to this stimulus compared with its solvent, water (T23 °C in the temperature series). An example of one of these is shown in Fig. 9 of neuron bo13 which had responses to Cap ($P<0.05$) and to taste ($F[5,22]=22.29$, $P<0.001$). Some of these neurons also responded to temperature (T10 °C, T37 °C and T42 °C) and/or taste (N). The responsiveness of the eight neurons with significant responses to capsaicin to different temperatures is shown in Table 3. This shows that the profiles of the responses of the capsaicin responding neurons were not very similar in general to each other, providing evidence that capsaicin is encoded by independent information channels to the other stimuli. Capsaicin is perceived to have a bitter taste (Green and Schullery, 2003). However, the neuronal responses to Cap were not very close to bitter in the multidimensional scaling (Fig. 8) or cluster analysis (Fig. 7). We showed in preference tests that the capsaicin was perfectly discriminable by the monkeys, and in fact they chose stimuli other than capsaicin.

The reconstructed positions of the neurons in this study are shown on Fig. 10. The uni- or multimodal re-

Table 3. Responses (in spikes/s) of capsaicin-responding neurons

	G	N	M	H	Q	T10 °C	T23 °C	T37 °C	T42 °C	Cap
Bk296	20.5	15.4	22.0	36.0*	23.0	39.5	10.3	39.7*	37.3*	36.7*
Bk299	4.8	12.5*	12.0*	12.0*	10.0*	3.3	1.7	10.3*	13.5*	9.5*
Bo13	3.8	38.6*	12.8*	7.0*	10.3*	3.4	4.0	4.5	5.2	17.3*
Bo17	8.3	14.8	9.0	6.0	6.0	6.5	8.6	4.6	7.0	2.0*
Bo18	10.0*	3.0	3.0	7.0	5.0	16.8*	3.6	9.8	8.6*	13.8*
Bo25	12.4	13.6	20.0*	18.0*	14.0	12.2	11.5	20.3*	15.2	19.5*
Bo27	0.3*	2.0*	1.0*	2.0*	4.0	21.6*	8.8	8.4	4.8	19.0*
Bo81	16.5*	3.6*	5.0	7.0	6.0	8.5	8.2	9.5	7.6	3.6*

* Significant response compared to T23 °C Water.

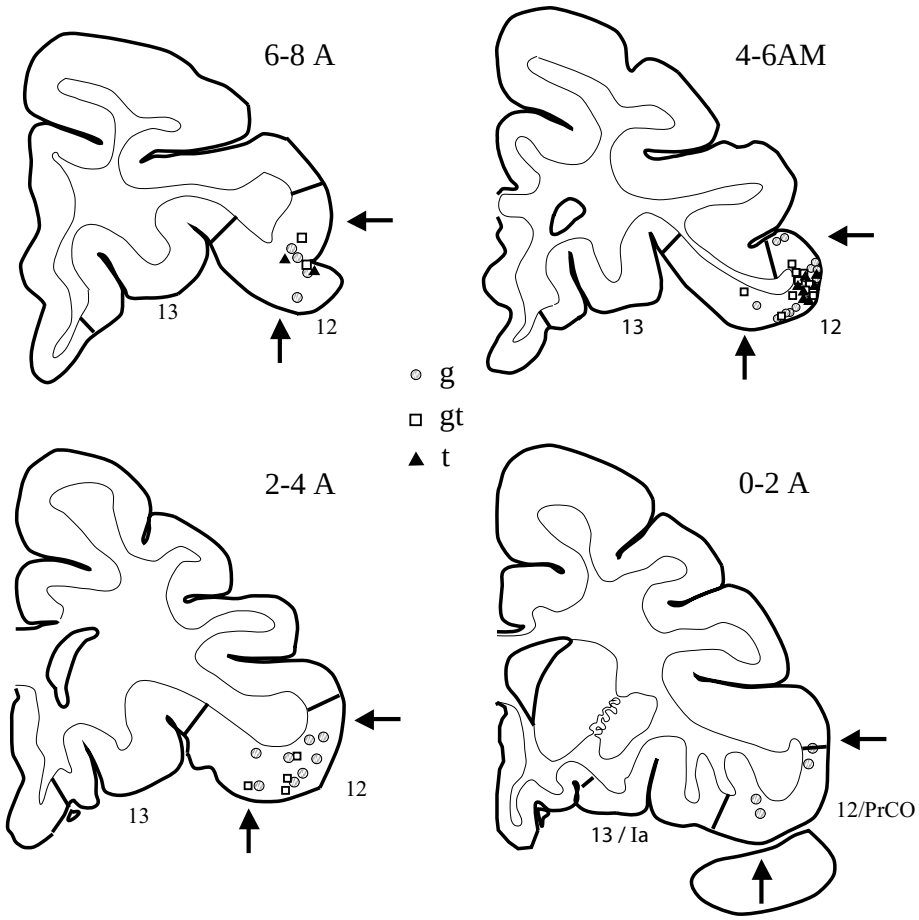

Fig. 10. The reconstructed positions of the neurons in this study. The symbol with which the location of each neuron is indicated shows whether the neuron was tuned to g=taste (circle), t=temperature (triangle), or to both taste and temperature (square). The neurons were located within the orbitofrontal cortical area; 6–8 A shows that the coronal section was taken 6–8 mm anterior to the sphenoid process used as a landmark (Aggleton and Passingham, 1981), and which is at approximately the A-P level of the optic chiasm. The arrows indicate the region within which the recordings were made.

sponses of the neurons are indicated by symbols. The temperature sensitive neurons discovered in this study are located in the caudolateral part of the OFC, in a similar region to gustatory neurons.

DISCUSSION

This study provides the first evidence we know on the responses of neurons in the primate OFC to the temperature of substances in the mouth, and indeed the first evidence on oral thermosensory neuronal responses in any cortical area in primates. The temperature response tuning profiles of the neurons (Fig. 6) showed that some were tuned to warm, some to cold, and that some responded to either warm or cold. These are the first oral temperature response tuning profiles of cortical neurons available for more than two temperatures in any species. The fact that many different response profiles were found in this set of neurons (see Fig. 6), shows that their responses reflected thermal sensitivity, and not any simple factor such as attention. Indeed, the responses profiles of the neurons, and the fact that these 26 neurons had very significantly different responses to different temperatures, shows that these neurons encode oral temperature. Moreover, none of these neurons responded to mouth movements. As a distributed representation (as shown by the breadth of tuning and sparseness, and reflected in the MD space shown in Fig. 8), this population of neurons is able to provide an accurate representation of the temperature of substances in the mouth. The fact that some are tuned to warm, and others to cold (see Fig. 6), may be adaptive in that different behavioral and thermoregulatory responses to warm and cold in the mouth are required, and having separate neurons for warm and cold may facilitate the output connections required to action systems to produce different responses.

The fact that the neurons have different response profiles to the temperature series (and do not all have for example monotonically increasing responses with increasing temperature) is part of the signature that the neurons convey at least partly independent information (Rolls and Treves, 1998; Rolls and Deco, 2002; Rolls et al., 2003d, 2004). In that the information is at least partly independent, the population of neurons can encode more information

than any one neuron. By encoding temperature what is signified is that information can be decoded from (i.e. "read out from") the neuronal responses about temperature. These concepts are described in more detail elsewhere (see above references and Franco et al., 2004).

The fact that some of the neurons described in this paper had unimodal temperature responses, that others have unimodal taste responses, and that others have unimodal somatosensory responses through a viscosity-sensitive channel (see Fig. 5) shows that there are inputs to the primate OFC that encode these sensory properties separately. This shows that the OFC provides an unambiguous and separate representation of each of these sensory properties, so that independent behavioral and regulatory responses can be made to each type of sensory property. In addition, some OFC neurons respond to combinations of these sensory inputs (see Figs. 2–5). These bimodal and trimodal representations could be formed by convergence onto single neurons in the OFC, or there could be convergence before the OFC. The fact that there is some convergence potentially allows for behavior to be specific to particular combinations of these inputs. For example, particular combinations of taste, temperature and texture might be pleasant, and be so either innately, or as a result of learning. Further, it is known that there are interactions between these sensory inputs, with for example sweet stimuli tasting sweeter at 50 than 22 °C (Schiffman et al., 2000), and perceived intraoral temperature depending on oral viscosity (Engelen et al., 2002). Another function of such combination-sensitive neurons could be in sensory-specific satiety, in that a particular combination of these sensory inputs might become less pleasant after eating the food to satiety partly because the particular set of combination-sensitive neurons shows adaptation (see further Rolls, 1999).

The temperature inputs to the OFC may reach it through the insula. Baylis et al. (1994) showed that there are direct projections from the insula to the part of the OFC in which we recorded in the current investigation. It is known that the temperature of the external body surface is represented in the mid part of the insula (Craig et al., 2000), although that representation may be more posterior in the insula than the region known to project to the lateral part of the OFC containing taste neurons from which we recorded. It is not possible to compare the responses of OFC neurons to oral temperature with those in any other cortical area to oral temperature, as this is the first report we know of the representation in any primate cortical area of oral temperature. Indeed, even in the rat (Yamamoto et al., 1981, 1988; Kosar and Schwartz, 1990a,b) and cat (Landgren, 1957; Tsuboi et al., 1993), there is very little evidence on this, with some neurons in the somatosensory areas reported as having oral temperature sensitivity. Even cortical temperature neuronal representations to non-noxious skin temperature stimuli have not been extensively described (Kreisman and Zimmerman, 1973 in the monkey; Tsuboi et al., 1993 in the cat). The most anterior part of the insula is the primary taste cortex in macaques (Yaxley et al., 1990; see Rolls and Scott, 2003), and we (Kadohisa et al., 2003) have been able to show in experiments completed to date in one macaque that this primary taste cortex contains unimodal temperature as well as taste neurons, and also bimodal taste and temperature neurons, so that this is very likely to be a source of inputs to the primate OFC temperature-responding neurons described here. It may be that oral temperature is represented in the anterior insula in the primary taste cortex, and possibly in a separate somatosensory area close to this (de Araujo et al., 2003), which are specialized to represent the oral cavity. On the other hand, it is also possible that there is some contribution from the more mid-insula area described by Craig et al. (2000) which receives inputs via the posterior part of the ventral medial nucleus of the thalamus (Craig et al., 1994, 2000). It will be of interest to determine whether the thermosensitive inputs to the primary taste cortex reach it through the taste thalamus (nucleus VPMpc), where some taste neurons in monkeys (Pritchard et al., 1989) and rats (Verhagen et al., 2003c) have thermal responsiveness, or whether there are other routes. In the periphery, it is known that chorda tympani fibers in the monkey (Sato et al.,1975) and hamster (Ogawa et al., 1968) show significant correlations between the responses to H and those to cooling (20 °C), and between the responses to sucrose and warming (to 40 °C). Some lingual nerve fibers in monkeys were activated by cooling to 15 °C but not by taste (Danilova and Hellekant, 2002). In the present study, no clear correlations between temperature sensitivity and sensitivity to particular taste stimuli were found.

Capsaicin was found to activate some neurons in the OFC. Peristimulus time histogram analyses showed that these neurons typically responded within 250 ms of application of the stimulus, and continued to respond for typically 2 s or more. The responses of individual capsaicin-sensitive neurons (e.g. Fig. 9), and the representation of capsaicin by the population of 26 neurons as shown in the multidimensional space in Fig. 8 and the cluster analysis in Fig. 7, show that capsaicin is represented differently from other somatosensory stimuli such as temperature in the range 10–42 °C, and most of the other stimuli. This shows that information about capsaicin is represented in the OFC via transmission channels that are separate from those used for temperatures in the range 10–42 °C and for the taste and most of the other oral stimuli. The use of capsaicin in these investigations thus reveals a separate type of oral representation in the OFC. The fact that the neurons activated by capsaicin were not activated by our warmest temperature stimulus (42 °C) is perhaps consistent with the finding that capsaicin (in the mouse) activates the VR1 receptor, which is also activated by increases in temperature above approximately 43 °C (Caterina et al., 1997, 1999; Patapoutian et al., 2003). (We did not explore higher temperatures because we did not wish to deliver potentially harmfully high temperatures to the mouth of our subjects.) It may be that the capsaicin system is especially involved in detecting noxious effects of hot temperature, and that the 42 °C warm stimulus used in the study described here did not activate that hot, noxious, sensing

system, but instead activated a separate "warm" system that encodes for stimuli that are frequently pleasant, especially when core temperature is low (Cabanac, 1971). (We note that the Trpv3 receptor is activated by temperatures above 33 °C, and the Trpv4 receptor by temperatures in the range 27–42 °C; Patapoutian et al., 2003.)

There is evidence that the primate OFC represents the reward value of many stimuli (Rolls, 1999, 2000, 2004). Some of the first evidence for this is that the primate OFC is an excellent site for brain-stimulation reward (Rolls et al., 1980), that brain-stimulation reward here is hunger-dependent (Mora et al., 1979) providing evidence that the electrical stimulation is activating a system that in part implements the reward value of food, that macaques learn to self-administer amphetamine to the OFC (Phillips et al., 1981), and that i.v. administration of amphetamine in humans activates the OFC as shown by fMRI (Völlm et al., 2004). It was then shown that single neurons in the primate OFC learn to respond, in one trial, to a visual stimulus associated with a taste reward, and that other neurons detect the mismatch between an expected reward based on the visual stimulus shown and the taste reward/punishment actually obtained (Thorpe et al., 1983). Then it was shown not just that there are taste neurons in the primate OFC (Rolls et al., 1990), which contains the secondary taste cortex in that it receives directly from the primary taste cortex (Baylis et al., 1994), but that these taste neurons encode the relative reward value of or preference for the taste, in that their responses gradually decrease to zero to a taste with which the monkey is satiated, but remain undiminished to other flavors which have not been fed in the meal (Rolls et al., 1989). The presence of neurons that reflect the relative reward preference of stimuli in the OFC has been confirmed by Tremblay and Schultz (1999). Indeed, such neurons are also present for the relative reward value of both olfactory and visual stimuli, as shown by sensory-specific satiety experiments for these sensory modalities too (Critchley and Rolls, 1996a). The same is found too in humans, in that feeding humans to satiety on one food decreases the pleasantness of the flavor of that food, and of activation in the OFC as shown by BOLD MR imaging, but the same reductions are not found for another food not eaten in the meal (Kringelbach et al., 2003). Neurons in the primate OFC also reflect the learned associations (Critchley and Rolls, 1996c), and the learning of associations (Rolls et al., 1996), between olfactory and taste stimuli, and something similar may be present in what may be a corresponding system in rodents (Schoenbaum et al., 1998). The OFC appears to be special in its representation of the reward value of taste, olfactory and visual stimuli, in that sensory specific satiety does not reduce neuronal responses in the primary taste cortex (Rolls et al., 1988; Yaxley et al., 1988), in the inferior temporal visual cortex (Rolls et al., 1977), and in that in humans activation of the OFC but not of primary cortical olfactory areas reflects the pleasantness of odors (Rolls et al., 2003b). These findings are among those on which a theory of the implementation of emotion in the brain has been built (Rolls, 1999). It could be that, in line with the functions of the OFC in representing the reward value and pleasantness of many stimuli (see Rolls, 1999, 2000), including olfactory (Rolls et al., 2003b), food flavour (Kringelbach et al., 2003), taste (O'Doherty et al., 2001a; de Araujo et al., 2003), somatosensory (pleasant touch to the hand; Rolls et al., 2003a), and monetary reward (O'Doherty et al., 2001b), the temperature-responding neurons described here are involved in the perceived pleasantness or unpleasantness of different temperatures in the mouth. Experiments to test whether the responses of the neurons described here to oral temperature depend on core temperature would provide evidence on this, which might then provide a neural basis for the fact that a warm drink is pleasant when we are cold, and a cool drink when we are hot. In any case, the results described here show that capsaicin is well represented in the primate OFC, but that there is no special convergence of the effects of capsaicin onto neurons concerned with temperature up to 42 °C. The convergence of capsaicin, temperature, viscosity, and taste effects onto some neurons in the OFC does provide for behavioral and subjective responses to particular combinations of these sensory inputs. (We note that the concentration of capsaicin we used, 10 μM, is well above the human recognition threshold which is 0.7 μM; Szolcsanyi, 1990.)

It is a feature of the OFC that relatively low proportions (typically several percent; see papers referred to above) of neurons are tuned to any one particular sensory modality such as taste, smell, oral texture, and vision. Within each of these sensory modalities, neurons can be quite sharply tuned, as illustrated in Fig. 6 for temperature. These properties mean that the representation of each modality is kept quite sparse over the whole population neurons. In addition, many OFC neurons respond to combinations of these sensory inputs, as illustrated by the responsiveness of the neurons described in this paper (see Fig. 5). These properties, taken together, may be particularly suitable for indicating with a relatively small number of active neurons exactly which sensory stimulus is in the mouth, and for ensuring that rather different populations of neurons are activated by oral stimuli that consist of either unimodal or different complex mixtures of these components. This is particularly appropriate for a brain system that implements sensory-specific satiety, for then a neurophysiological property as simple as synaptic adaptation after several minutes of stimulation can compute the reduced (hedonic) response to one stimulus compared with another, even when they have overlapping components (Rolls et al., 1989; Critchley and Rolls, 1996a; Rolls, 2000; Rolls and Scott, 2003).

In conclusion, the data presented in this paper provide the first evidence that OFC neurons can be specifically tuned to oral temperature, and show that this type of somatosensory input can be combined with somatosensory inputs produced through viscosity-sensitive information channels (Rolls et al., 2003c), and with inputs produced by capsaicin. These are in addition to separate somatosensory inputs described previously that allow fat (Rolls et al., 1999; Verhagen et al., 2003b) and astringency

(Critchley and Rolls, 1996b) to be represented independently of the three somatosensory information channels described here. In addition to these separate representations provided by some neurons, other neurons respond to combinations of temperature and taste, viscosity, and/or capsaicin. The representation of oral temperature was independent of that to taste, and of that to capsaicin. This evidence indicates that a rich representation of many of the sensory properties of food in the mouth is represented in the OFC, with each property being represented separately as well as by combination-encoding neurons. There is already evidence that at least some of these representations are important in representing the pleasure produced by these types of sensory input (see references above), and to these can be added the new representation described here of the temperature of substances in the mouth. This representation of temperature is likely to be involved in the regulation of food and fluid intake, and in thermoregulation. Moreover, dysfunction of this system in the OFC is likely to lead to abnormal sensations produced by oral stimuli.

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