Review

Temporal coding in the gustatory system

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Abstract

Hallock, R.M. and Di Lorenzo, P.M. [2006. Temporal coding in the gustatory system. Neurosci. Biobehav. Rev. XX(X) XXX–XXX]. Early investigations of temporal coding in the gustatory system showed that the time course of responses in some neurons showed systematic differences across the various classes of taste stimuli, implying that the temporal characteristics of a response can convey information about a taste stimulus. Studies of temporal coding in the gustatory system have grappled with several unique methodological challenges, including the quantitative description and comparison of temporal patterns as well as the assessment of the relative contributions of spatial and temporal coding to the information contained in a response to a tastant. Other investigations have suggested that the cooperative activity among synchronously firing ensembles of taste-responsive neurons at all levels of processing in the brain can convey information about taste quality (sweet, sour, salty, bitter and umami). Behavioral studies using patterned electrical stimulation of the brain in awake animals have supported the idea that temporal coding of taste stimuli may have functional significance.
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1. Introduction

In the past several years, the study of sensation and perception has been energized by the discovery that some, if not all, sensory systems utilize the temporal parameters of neural responses to convey information about stimuli (e.g. see Lestienne (2001) for a recent review). These discoveries have recast our understanding of neural

communication in nearly all sensory modalities, including the chemical senses. For example, in the olfactory system, it has been shown that organized oscillations in firing patterns of neurons in the central nervous system of moths are not only correlated with olfactory discrimination (MacLeod et al., 1998) but are necessary for some fine discrimination to take place (Nusser et al., 2001; Stopfer et al., 1997). Collectively, such data can be used to assert the functionality of temporal coding, and thus its relevance to neural processing of sensory stimuli. In this context, the taste system is an attractive model for the study of temporal coding because there are relatively few categories of similar tasting stimuli, called the "basic" taste qualities (sweet, sour, salty, bitter and possibly umami), and because the successful encoding of taste stimuli can often be gauged by both innate and learned behavioral reactivity.

Here we define "temporal coding" as any neural representation in which the distribution of neural activity over time contains information about a stimulus that is meaningful to an organism. For example, information about taste quality could be conveyed by systematic changes in the firing rate over time (i.e. the rate envelope or time course) within a response, by the timing of spikes during the response (Di Lorenzo and Victor, 2003), or by the frequency distribution or particular sequence of interspike intervals during the response. Temporal coding may be contrasted with "spatial coding" in that a spatial code relies on the identity of a neural element to convey information, e.g. two stimuli evoke responses in different subsets of cells. "Population coding," where all neurons in a population contribute to the code for a given stimulus, would be one example of spatial coding. This might take the form of a population vector constructed by the weighted average firing rates across neurons that would specify the identity of a stimulus (Georgopoulos et al., 1986; Nicolelis and Chapin, 1994; Wilson and McNaughton, 1993). Obviously, both spatial and temporal coding may be utilized by the same population of neurons.

The definition of temporal coding can be broadened to include the interactions among neurons as a source of information. Coincident firing of one or more neurons, for example, may convey information about a taste stimulus. In this regard, Katz et al. (2002a, b) have shown that small groups of cortical neurons form cohesive ensembles by firing synchronously during a response to a tastant. Because these dynamic ensembles convey information both by virtue of the timing of their spikes, i.e. simultaneous with respect to each other, and by their identity, i.e. different ensembles are formed according to the particular tastant, this type of representation would be an example of a "spatiotemporal" code.

The idea that temporal coding might be used by the gustatory system originated from the observation that different tastants can evoke neural responses of equal magnitude but with different temporal patterns of firing both across neurons and in a single neuron (Mistretta, 1972). For example, in Fig. 1, responses to sucrose and
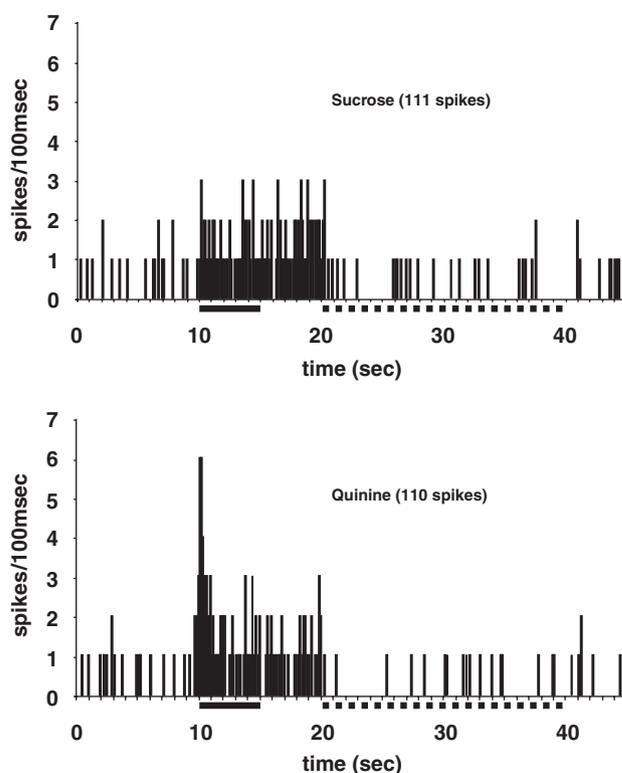

Fig. 1. Peristimulus-time histograms (PSTHs) of responses to sucrose (top) and quinine (bottom) recorded from a single cell in the NTS of an anesthetized rat (Di Lorenzo and Victor, 2003). For each PSTH, the number of spikes in successive 100 ms bins over the time course of the response is shown. The number of spikes that occurred between the onset of the stimulus and the onset of the distilled water rinse is indicated in parentheses for each stimulus. Solid line indicates presence of the stimulus on the tongue and dashed line indicates distilled water rinse.

quinine are shown from a cell recorded in the nucleus of the solitary tract (NTS), the first synapse in the central pathway for taste in the rat (Di Lorenzo and Victor, 2003). It can be seen that each stimulus evokes a different temporal pattern of firing, even though the number of spikes over the response interval are nearly identical. Such observations have fueled several decades of investigation and speculation about the significance of the temporal parameters of taste responses in the neural representation of taste stimuli.

2. Neural coding of taste—what is encoded?

In the study of neural coding in the gustatory system, it is necessary to define what properties of a stimulus the system must encode, a task that is not nearly as straightforward as one might expect. Consider, for example, taste quality. It has been argued that each of the basic taste qualities represents a taste "primary" in the sense that any gustatory sensation could, in theory, be analyzed and reconstructed as a combination of these basic taste qualities. The most active challenge to this idea has been offered by Erickson (2000) and Schiffman (2000) who assert that taste stimuli can be arranged along a

continuum, rather than parceled into discrete groups. Because exemplars of the basic taste qualities are easily discriminable from each other, it seems reasonable to investigate the neural coding mechanisms that underlie these distinctions.

Intensity is another characteristic that is encoded by the taste system; in gustation, stimulus intensity is correlated with stimulus concentration. Most often, as the concentration of a taste stimulus increases so does the firing rate of the taste-responsive cell (Nakamura and Norgren, 1991; Nishijo and Norgren, 1990; Scott and Perrotto, 1980). So, as in other sensory systems, it would seem that information about stimulus intensity is transmitted by a rate code. However, given that most taste-responsive neurons respond to more than one of the basic taste qualities, for any given neuron there are portions of the intensity-response functions for tastants of different qualities where the average firing rates are identical. This renders response magnitude an ambiguous signal in all but the most narrowly tuned cells. In addition, as the stimulus concentration is increased, the number of responsive cells also increases (Funakoshi and Ninomiya, 1977; Ganchrow and Erickson, 1970) and there are occasions where the quality of a tastant varies with changes in concentration. For example, a low concentration of salt can evoke a sweet sensation (Bartoshuk et al., 1978; Dzendolet and Meiselman, 1967; Ossebaard and Smith, 1995).

Multiplexed with quality and intensity in the neural response to a tastant is its hedonic value, that is, its pleasant or aversive tone. This property is not an intrinsic characteristic of the stimulus per se, but is rather the result of the dual influences of genetics and experience. Thus, it is possible to compare the neural responses of those stimuli that are naturally preferred or avoided as well as those whose hedonic value has been altered by conditioning.

3. Temporal coding in relation to other theories of neural coding in gustation

Historically, there have been two major theories of neural coding in the taste system that have dominated the literature. These are the labeled line and across fiber (or neuron) pattern theories. Both of these theories are focused on the spatial representations of neuronal activity, and each can be contrasted with representations that incorporate temporal dimensions of the neural response. In spatial coding theories, the identity of the responsive neural elements and the magnitude of response (firing rate across the response interval, arbitrarily defined) are thought to convey information about stimulus quality and/or intensity. For example, in the labeled line theory (Frank, 1973, 1974), different taste qualities are encoded by separate groups of cells that respond exclusively, or at least maximally, to a specific quality. Taken to its extreme, the activity in non-overlapping groups of neurons would each represent different taste qualities. Because most taste-responsive cells at all levels of the nervous system respond to stimuli representing more than one taste quality, proponents of the labeled line theory argue that neurons that encode a given taste quality are those that respond most vigorously to exemplars of that quality relative to other taste qualities. These cells are then identified by their "best" stimulus among representatives of the basic taste qualities. In support of this theory are observations that the best stimulus of a cell is a good predictor of the relative response rates to the other, non-best stimuli (Frank, 1973, 1974), implying that each best stimulus category represents a neuron "type." In addition, experimental manipulations that selectively affect the behavioral reactivity to a single taste quality, such as conditioned taste aversion (Chang and Scott, 1984) or sodium deprivation (Contreras, 1977; Contreras and Frank, 1979; Scott and Giza, 1990), are known to affect only the appropriate class of best-stimulus cells. Another example of a spatial code is the across fiber (or neuron) pattern theory (Erickson, 1963; Pfaffmann, 1941, 1959). In that view, the relative response magnitude across the population of taste-responsive cells is thought to convey identifying information about taste stimuli. This conceptualization is based on the fact that in multisensitive cells, i.e. cells that respond to more than one taste quality, unambiguous identification of a taste stimulus cannot be gleaned from the simple presence or absence of a response. So, for example, two tastants of different qualities might evoke similar response rates depending on the particular concentrations at which they are presented. As a result, the relative response magnitude across multiple units may be a better means of stimulus identification. Indeed, it has been shown that across neuron patterns of responses evoked by similar tasting stimuli are highly correlated and those evoked by dissimilar tasting stimuli are poorly correlated (Doetsch and Erickson, 1970; Erickson, 1963; Ganchrow and Erickson, 1970). Additionally, behavioral measures of similarity have been shown to correspond closely to quantitative measures of across neuron pattern similarity (Scott, 1974), adding further credibility to this theory.

Both the labeled line and the across fiber pattern theories depend on a measure of relative response magnitude, most often calculated as the number of spikes occurring in some arbitrary interval (usually 3–5 s) during which the stimulus is present on the tongue (see Di Lorenzo and Lemon, 2000, for a discussion on this topic). Therefore, according to both theories, information about taste quality depends on some sort of rate coding, where information about a stimulus is represented by changes in the frequency of firing during stimulus presentation compared with the firing frequency over the same time period in the absence of a stimulus (spontaneous rate). It is easy to see how different stimulus properties might be confounded in multisensitive cells using only a rate code, even if the response magnitudes across the population are considered. Additionally, because the response interval is necessarily arbitrary (taste responses sometimes do not persist for the entire stimulus presentation or sometimes outlast the stimulus presentation), rate coding inherently ignores any systematic,

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potentially meaningful changes in firing rate that occur on a finer time scale.

Recent studies of genetically altered mice have provided powerful support for the idea of a labeled line code (see Scott (2004) for a review). These studies suggest that there are separate neural pathways associated with the perception and behavioral "attraction" associated with sweet stimuli (Zhao et al., 2003) and the perception and behavioral "avoidance" associated with bitter stimuli (Chandrashekar et al., 2000; Mueller et al., 2005). Moreover, genetic knockout mice with deletions of the receptors encoding sweet or bitter tastants also show selective respective deficits in the responses of peripheral nerves to these stimuli (Chandrashekar et al., 2000; Zhao et al., 2003). Remarkably, when peripheral taste receptor cells normally expressing receptors for sweet tastes are made to express bitter receptors, animals showed an avid preference for normally avoided bitter tastes (Mueller et al., 2005). The implication of these data is that taste quality is encoded through a dedicated labeled line that originates at the level of the receptor cell and is preserved throughout the central circuitry. This conceptualization is difficult to reconcile with what is known about the central gustatory pathways, e.g. divergence of peripheral afferents as they project centrally, multiple recurrent pathways across taste-related structures, nearly ubiquitous multisensitivity across taste qualities, etc. However, the circuitry that underlies the link between an apparently unambiguous signal arising from the periphery to the generation of a set of behaviors as complex as taste preference remains the subject of investigation along multiple fronts. In this regard, the contribution of a temporal code may be to add information to an anatomically based (spatial) information channel or to define temporally based information channels among groups of multisensitive neurons.

4. A synopsis of gustatory neuroanatomy in relation to temporal coding

To orient the reader who may not be familiar with the anatomy of the gustatory system, we offer an overview of the mammalian gustatory system with annotations concerning the potential origins of distinctive temporal mechanisms of neural coding.

Groups of 50–150 taste receptor cells are aggregated in taste buds located in specialized structures on the tongue called papillae (Hamilton and Norgren, 1984). In the rat, fungiform papillae each contain one taste bud, and are located on the tip of the tongue (McLaughlin and Margolskee, 1994). Foliate papillae are formed by a series of grooves on the lateral portion of the posterior tongue, each containing numerous taste buds (McLaughlin and Margolskee, 1994). The rat has one circumvallate papilla, located on the medial part of the most posterior portion of the tongue (Firestein et al., 1999). Like foliate papillae, the circumvallate papilla contains numerous taste buds.
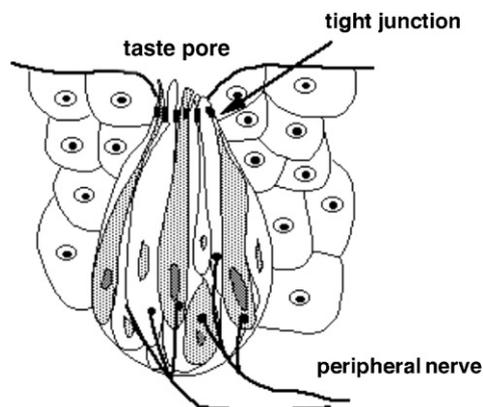

Fig. 2. A schematic diagram of the structure of the taste bud showing light and dark taste receptor cells, surrounding epithelial cells and peripheral nerve innervation. (reprinted from Di Lorenzo and Youngentob (2002) by permission).

The very first opportunity for systematic variation in the temporal pattern of response associated with different tastants occurs in the taste receptor cell. Within each taste bud, there are several types of taste receptor cells, only a minority of which are innervated by peripheral nerve fibers (Murray, 1986; see Fig. 2). Slender cilia protrude from the apical end of taste receptor cells into the oral environment through the taste pore. Tight junctions between taste receptor cells prevent taste stimuli from entering the taste bud. There are generally three types of taste receptor cells described in mammalian taste buds: Type I (dark), Type II (light) and Type III, which synapse on the gustatory nerves. These cell types represent different developmental stages; taste receptor cells are known to have a life span of about 10 days. In mouse, all types of taste cells receive synapses from gustatory nerve fibers (Royer and Kinnamon, 1994).

The presence of different transduction mechanisms in the same taste receptor cell is consistent with the idea that different tastants may produce responses with different time courses. Molecules of taste stimuli interact with receptors located in the membranes of the taste receptors. NaCl and HCl both stimulate taste receptor cells through direct activation of ion channels, but sucrose and quinine transduction utilize second messenger systems, which are inherently slower than ionotropic receptor mechanisms (Gilbertson et al., 2000). Depolarization in taste receptor cells produces action potentials which then drive activity in the peripheral taste nerves (see Herness (2000) and Herness and Gilbertson (1999) for recent reviews). Though stimuli from each of the basic taste qualities stimulate different transduction mechanisms, most taste receptor cells respond broadly across taste qualities (Gilbertson et al., 2001; but see Zhang et al., 2003 for contradictory evidence). For example, the commonly described phasic–tonic patterns of response in the CNS (see below) have also been observed in the taste receptor cell itself (Sato, 1977) and there is evidence that different phasic–tonic relationships may be

associated with different taste qualities (Kinnamon and Cummings, 1992). On the other hand, neural network analyses of the spike trains arising from single taste buds in the hamster have shown that differences in the average rate of firing, especially in the first 1 s of response, can be used to distinguish between NaCl versus sucrose or NC-01, an artificial sweetener (Varkevisser et al., 2001). This distinction was independent of stimulus intensity.

In the basal portion of the taste bud in the rat, nerve fibers form a dense plexus, sending thin beaded branches between the taste cells to synapse on Type III cells (Kanazawa and Yoshie, 1996; Muller and Jastrow, 1998). It is typical for 3–5 taste receptor cells to be innervated by a single afferent fiber (Kinnamon et al., 1988). Navigating the interface between the taste receptor cells and the afferent nerves are numerous neurotransmitters, including glutamate, GABA, acetylcholine, norepinephrine and serotonin. In addition to a complex array of neurotransmitters and their potential interactions, there are abundant opportunities for interactions among papillae (Miller, 1974; Vandenbeuch et al., 2004) subserved by the extensive branching of the fibers of the afferent nerves innervating the taste buds (Miller, 1971). This arrangement implies that the signals generated by taste stimuli are highly processed by the time they reach the peripheral nerve fibers. Thus, receptor kinetics associated with a given tastant may not be the only factor contributing to the temporal pattern of firing in afferent taste nerves.

Taste buds located in the oropharyngeal area are innervated by three cranial nerves. The facial nerve (cranial nerve VII), innervates taste buds through two branches: The greater superficial petrosal nerve innervates taste buds in the nasoincisor ducts and palate, while the chorda tympani (CT) nerve innervates taste buds on the rostral 2/3 of the tongue. Cell bodies of the gustatory fibers of the facial nerve are located in the geniculate ganglion. The lingual branch of the glossopharyngeal nerve (cranial nerve IX) innervates taste buds on the caudal 1/3 of the tongue. The cell bodies of the gustatory fibers of the glossopharyngeal nerve are located in the petrosal ganglion. Taste buds on the epiglottis are innervated by the superior laryngeal branch of the vagus nerve (cranial nerve X), with cell bodies in the nodose ganglion.

Cranial nerves VII, IX and X terminate within the rostral portion of the NTS in a caudal to rostral topography, respectively (Halsell et al., 1993; McPheeters et al., 1990; Travers and Norgren, 1995). This segregation of the various projections underlies an orotopic map of taste responses in the NTS. Such an arrangement may form the basis for spatio-temporal variations in taste responses given the spatial pattern of taste stimulation during natural licking and the observation that each nerve appears to show differential sensitivity across the basic taste qualities. Specifically, the greater superficial petrosal nerve is known to be especially responsive to sweet stimuli (Travers and Norgren, 1991; Travers et al., 1986), the chorda tympani especially responsive to NaCl and acid (Frank, 1973, 1974;

Frank et al., 1983, 1988) and the glossopharyngeal nerve especially responsive to quinine (Frank, 1991; Hanamori et al., 1988), though each nerve responds to all of the basic taste qualities to some extent.

Cells in the rostral part of the NTS of rodents are known to have both ascending and descending projections, which collectively provide the basis for taste identification and discrimination as well as a rich interface with motivational and behavioral systems involved with ingestion. Except in the primate taste system (see Pritchard, 1991), the primary target of cells in the NTS is the parabrachial nucleus of the pons (PbN; Norgren, 1974; Saper and Loewy, 1980). (In primates, taste-related projections from the NTS bypass the PbN.) Only about one third of the taste-responsive NTS cells in the rat send axons to the PbN (Monroe and Di Lorenzo, 1995; Ogawa et al., 1982, 1984; Ogawa, and Kaisaka, 1980) though recent electrophysiological evidence in the hamster suggests that this might be an underestimation (Cho et al., 2002). Even so, the time course of taste responses in the NTS and PbN are remarkably similar (Di Lorenzo and Monroe, 1997; Fig. 3). Other taste-sensitive projections from the NTS terminate in the paraventricular hypothalamus, dorsal motor nucleus of the vagus, the salivatory nucleus and the nucleus ambiguus (Horst et al., 1989; Norgren, 1985; Ricardo and Koh, 1978). The descending projections of NTS target the medullary reticular formation, including the parvocellular reticular nucleus, the intermediate reticular nucleus and the dorsal medullary reticular nucleus (Beckman and White-head, 1991). Projections to reticular formation nuclei are important in jaw movements (Nishimuta et al., 2002) and orofacial gestures signaling rejection (DiNardo and Travers, 1997).
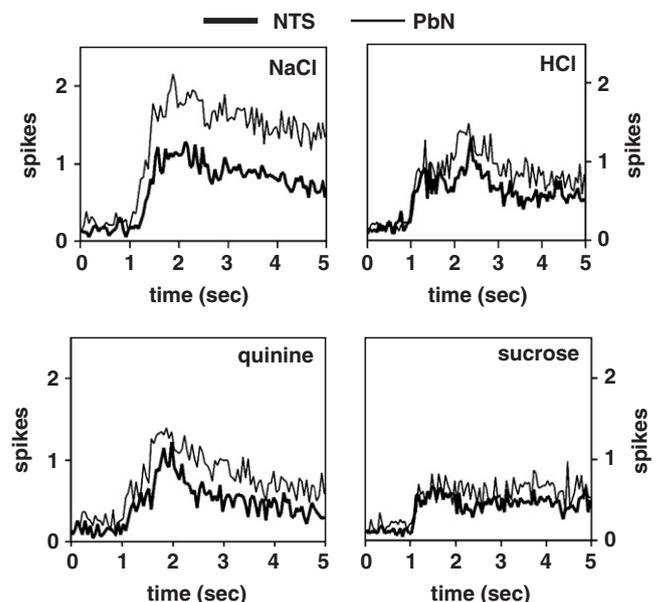

Fig. 3. Average time course of response to representatives of the basic taste stimuli recorded simultaneously in the NTS and PbN of anesthetized rats. Time bins were 50 ms. Taste stimulus is presented at 1 s. Reprinted from Di Lorenzo and Monroe (1997) by permission.
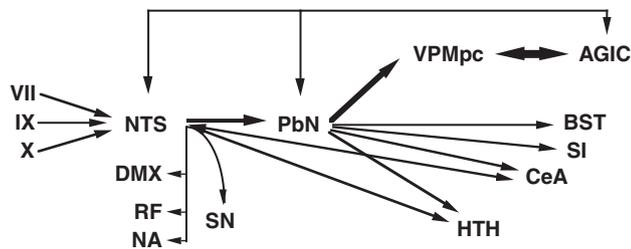
Fig. 4. A schematic diagram of the anatomical pathways associated with taste in the rat brain. Thick lines indicate the main ascending pathway for gustatory information. Abbreviations are as follows: VII, facial nerve; IX, glossopharyngeal nerve; X, vagus nerve; NTS, nucleus of the solitary tract; PbN, parabrachial nucleus of the pons; VPMpc, ventroposteromedial nucleus of the thalamus, parvocellular region; GC, gustatory cortex; CeA, central nucleus of the amygdala; HTH, hypothalamus; BST, bed nucleus of the stria terminalis; SI, substantia innominata; RF, reticular formation; DMX, dorsal motor nucleus of the vagus nerve; NA nucleus ambiguous; SN, salivatory nucleus.

In rats, gustatory neurons in PbN project rostrally in the central tegmental bundle and terminate bilaterally in the parvicellular region of the ventromedial thalamus (VPMpc) (Bester et al., 1999; Karimnamazi and Travers, 1998; Krout and Loewy, 2000; Norgren, 1974). In addition, ascending fibers from the PbN also project to the gustatory neocortex (GC; Saper, 1982), lateral hypothalamus (Bester et al., 1997), central nucleus of the amygdala (Bernard et al., 1993; Karimnamazi and Travers, 1998), substantia inno-minata (Karimnamazi and Travers, 1998), and the bed nucleus of the stria terminalis (Alden et al., 1994). From the VPMpc, there is a reciprocal connection with the gustatory neocortex (Norgren and Grill, 1976; Wolf, 1968). The gustatory neocortex in rodents is located in the agranular and dysgranular insular cortex, on either side of the middle cerebral artery, dorsal to the rhinal fissure. Cells in the insular cortex receive convergent input from multiple peripheral nerves (Hanamori et al., 1997) and thus integrate taste sensations from all areas in the oral cavity (see Fig. 4).

Like all sensory systems, the gustatory system is characterized by a rich centrifugal influence, providing the opportunity for modulation and modification of the ascending signal. For example, the gustatory neocortex projects to the amygdala (Norgren and Grill, 1976; Shi and Cassell, 1998), back to the PbN (Lasiter et al., 1982; Norgren and Grill, 1976; Wolf, 1968) and back to the NTS (Norgren and Grill, 1976; Whitehead et al., 2000), in addition to its main output to the VPMpc. The lateral hypothalamus also sends direct input to the PbN and the NTS (Bereiter et al., 1980; Hosoya and Matsushita, 1981; Whitehead et al., 2000), and projections from the amygdala to the NTS have been described (Whitehead et al., 2000). The highly interconnected nature of the gustatory system presents the opportunity for numerous recurrent loops that may underlie the complex temporal structure that has been described in cortical responses to taste (Katz et al., 2002a, b, and see below).

5. Methodological issues impacting the study of temporal coding in the gustatory system

Prerequisite to any assertion that the precise temporal characteristics of a taste response convey information about a stimulus is the determination of the stability of the response with simple repetition. Factors such as the failure of synaptic transmission, activity in other brain regions, and the spontaneous activity of a neuron can all affect the reliability of specific response patterns (Lestienne, 2001). Although some types of temporal coding, e.g. interspike interval distribution, might be robust against variability in response magnitude, most mechanisms of temporal coding require the response to be replicable along some dimension. In this context, the idea of temporal precision can be defined as a measure of the limits of variability in the temporal domain that can be tolerated without loss of information. In the face of highly variable responses, many repetitions of the stimulus may be required to reveal the critical temporal parameters of the response. For example, the timing of certain spikes in taste-evoked spike trains may be more important than others for taste quality coding and may only be identifiable across repeated responses.

The most common stimulus presentation procedures used to study taste in the nervous system generally preclude the quantification of response variability. That is, unlike studies of vision or audition, where stimuli might be presented dozens of times, in studies of taste, stimuli are typically presented at most two or three times. Taste stimuli are usually presented for at least 3 s, and must be rinsed off the tongue for several seconds to prevent adaptation (Smith and Bealer, 1975). Interstimulus intervals are at least a minute or two, adding to an already lengthy protocol, given that at least four or five different stimuli must be tested for even a basic assessment of a cell's response properties.

There have been only two studies that have had taste response variability/reliability as their focus. The first of these studied the responses to taste stimuli in CT nerve fibers. Ogawa et al. (1973) examined the responses of eight individual CT fibers in the rat to presentations of five tastants, each presented six times. Four of these taste stimuli were prototypical tastants representing the four basic taste qualities, i.e. sweet, sour, salty and bitter. Results showed that while response magnitude could vary, occasionally so much so that the relative effectiveness among taste stimuli was changed, the temporal character-istics, i.e. interspike interval (ISI) histograms and autcor-relograms, of taste responses generally remained relatively constant across stimulus repetitions. In a second, more recent study, Di Lorenzo and Victor (2003) recorded electrophysiological responses from cells in the NTS of the rat to as many as 27 repetitions of the four basic taste stimuli and found wide variability in the response magnitude to a given tastant across trials. The response profile, defined as the relative response rates across tastants, of roughly half the cells changed with repetition,

in some cases so much so that the best stimulus of the cell differed across trials. Since a change in the best stimulus would imply a different role for that cell in the neural code for a tastant, these findings beg the question of which aspects of a taste response would provide the basis for a stable representation of a taste stimulus. Interestingly, those cells that showed the most variable response magnitudes with stimulus repetition were also the cells whose responses showed evidence of temporal coding, as described below.

Two additional issues in the analysis of temporal coding are how to mathematically describe the temporal pattern of a response and how to differentiate among temporal patterns elicited by different stimuli. In general, it is easier to measure the similarity of two temporal patterns than to quantify the temporal characteristics of a single response. A large part of the problem lies in knowing what feature(s) of the temporal pattern of response might be critical. In many investigations, researchers have offered verbal descriptions of peristimulus time histograms (PSTHs) derived from the responses to the various stimuli as evidence of temporal coding of taste (Perrotto and Scott, 1976). Similar descriptions of dot rasters (Katz et al., 2001) or the sequence of interspike intervals (Funakoshi and Ninomiya, 1977) associated with taste responses have also been published. In many cases the averaged PSTH across the entire sample of cells is used as the object of analysis (Scott and Perrotto, 1980; Verhagen et al., 2003). Quantitative comparisons of different temporal patterns are often made using standard statistical techniques such as correlation (Scott and Mark, 1986), fast Fourier transformations (Katz et al., 2001) or chi-square (Katz et al., 2001), or extensions of these measures such as multidimensional scaling or principal components analyses (Di Lorenzo and Schwartzbaum, 1982). Recently, some computational techniques developed for use in other sensory systems have been applied to data from the gustatory system (Di Lorenzo and Victor, 2003; Katz et al., 2001, 2002a, b); these techniques will be discussed later.

To quantify temporal patterns of taste responses in the NTS and PbN, Erickson et al. (1994) utilized fuzzy sets. This conceptualization can be contrasted with traditional organizational methods as follows: In most categorization schemes that have been applied to taste responses, groups of cells are formed based on the similarity of their response profiles across tastants. Any particular cell can belong to only a single group, so that each group consists of a collection of cells that do not overlap in membership with any other group. Such a grouping of cells is called a "crisp set" to reflect the fact that membership in any one group is "all-or-none." Once grouped, the response properties of the cells in each group can be examined and the group labeled by the commonalities among them, e.g. NaCl specific, or HCl generalist (see Frank, 2000, for example). Like crisp sets, fuzzy sets are collection of cells with similar response properties. However, a given cell can belong to any group *to varying degrees*, so that membership is

"graded." In that way, fuzzy sets can be labeled by general response properties, e.g. robust responsiveness to NaCl accompanied by a weak response to quinine, and each cell's response profile can be assessed as to how closely it reflects that property. In the application of fuzzy sets to the analysis of temporal patterns of response, Erickson et al. (1994) derived four prototypical temporal patterns from the responses to representatives of the basic taste qualities recorded in the rat NTS and the PbN. A mathematical method called the "grade of membership" technique (in some ways similar to principal components analysis; Woodbury et al., 1978) was used to construct the four temporal patterns that identified each fuzzy set and to quantify, i.e. assign a weight to, the degree to which each response was associated with each set. Temporal patterns of individual taste responses could then be reconstructed using a linear combination of the four-prototypical temporal patterns scaled according to their weights. This methodology has the advantage that it makes no assumptions that different classes of stimuli necessarily evoke similar temporal patterns of response or that every cell uses the same temporal pattern of response to convey information about a given stimulus. Erickson et al. (1994) speculate that different receptor processes may underlie these prototypical temporal patterns.

One final methodological issue of note is how to parse the contributions of spatial and temporal coding, given the likelihood that taste responses utilize more than one type of coding mechanism to represent various aspects of a taste stimulus. An early attempt at this can be seen in the work of Mark and Scott (1985) and Scott and Mark (1986). In those studies, two multidimensional scaling analyses were applied to taste responses in the NTS of the rat. The first of these, meant to assess spatial coding, was based on interstimulus correlations of the response magnitude measured over the first 5 s of response across cells. The second analysis, designed to assess the contribution of temporal coding, was based on the interstimulus correlations of the temporal patterns of response to each tastant. (The temporal pattern of response was measured for each stimulus across cells as the average response rate in successive 100 ms time bins for 5 s.) Based on the results of these analyses, the authors argued that some pairs of stimuli could be best discriminated using a spatial code while others relied more heavily on information in the temporal pattern of response. For example, sucrose (sweet) and quinine (bitter) were well-differentiated (defined by low interstimulus correlations) with either spatial ($r = -0.19$) or temporal ($r = -0.26$) information whereas NaCl (salty) and $CaCl_2$ (mostly bitter; Tordoff, 1996) were differentiated more successfully by a spatial ($r = 0.55$) than a temporal representation ($r = 0.86$). In contrast, strychnine and citric acid (bitter and sour, respectively) were better differentiated by temporal ($r = 0.42$) than spatial ($r = 0.91$) information.

More recently, Di Lorenzo and Victor (2003) utilized the metric space method of Victor and Purpura (1996, 1997) to

characterize the contribution of the temporal structure of a response to discrimination of representatives of the four basic taste qualities. Electrophysiological responses to taste stimuli were recorded in 19 cells in the NTS of anesthetized rats where stimuli were repeated between 8 and 27 times. Briefly, the contribution of spike count (rate coding), spike timing and the sequence of interspike intervals to discrimination of taste stimuli were evaluated by a family of metrics designed to measure the distance, i.e. dissimilarity, between two spike trains by calculating the "cost" of transforming one spike train into the other. To measure the distance between two spike trains in terms of spike count, spikes were added or subtracted as necessary to one spike train until it contained the same number of spikes as the other. The cost was set at 1.0 for each spike added (or deleted). So, for spike count, the distance between two responses was simply the arithmetic difference between the number of spikes contained in each spike train. Similarly, for the distance in terms of spike timing or the sequence of interspike intervals, spikes in one spike train were added or deleted *and moved in time* until the temporal pattern of one spike train was identical to that of the other spike train. Here, the cost of adding or deleting a spike was 1.0, as with spike count, but the cost of moving a spike in time was calculated at a variety of levels of precision, measured by a parameter called "q." The cost of moving a spike (or interspike interval) by an amount of time t is set at qt where q is in units of $1/s$ (see Di Lorenzo and Victor, 2003 for further details). For each metric, the information conveyed at various values of q is calculated, and the value of q at which information is maximized is obtained. Importantly, there were several additional analyses that served as controls for the possibility of spurious results. Results showed that in addition to the number of spikes, spike timing was significantly correlated with discrimination of taste qualities in 10 of 19 (53%) cells. The contribution of timing information was especially notable during the initial 2 s of the response.

6. Information conveyed by the time course of a taste response

One of the basic characteristics of the time course of a taste response is its latency relative to the moment of stimulus-receptor contact. In most applications, the precise timing of this event can only be estimated. Moreover, given the extent of interaction among afferent nerve branches innervating the taste buds (Miller, 1971), it is difficult to determine the precise beginning of a response in any neural element besides an individual taste receptor cell. In those cells, differences in transduction mechanisms undoubtedly affect response latencies, and these may be reflected in the latencies of response downstream. Not surprisingly, then, a number of studies have reported that tastants of different qualities evoke responses at consistently different latencies. In rat CT nerve fibers (Pritchard and Scott, 1982) and cortex (Yamamoto et al., 1984), for example, the responses

to sugars and amino acids have been reported to occur with the longest latency relative to responses from other taste stimuli. In fMRI studies of human cortex, Na Saccharin was found to evoke a longer latency response than NaCl (Kobayakawa et al., 1996, 1999). Also, response latencies have been found to be longer in very young animals and to shorten as development progresses (Bradley and Mistretta, 1980). These latency differences most likely correspond to differences in the transduction mechanisms, or other peripheral processes for each class of taste stimuli. Given the extensive convergence of tactile and gustatory information in the CNS (Ogawa et al., 1984), it is certainly possible that the nervous system is capable of utilizing the lag between the arrival of tactile and gustatory signals to extract information about a taste stimulus. Various latencies for the different taste qualities may be used to identify tastants, or at least distinguish among tastants, within different time frames (Di Lorenzo et al., 1994; Di Lorenzo and Schwartzbaum, 1982).

Orderly changes in firing rate over the response interval have also been reported to contain stimulus-related information. Most taste responses show an initial, brief "phasic" portion where the firing rate is relatively high, followed by a sustained "tonic" component where the firing rate is diminished but remains higher than the spontaneous rate. This response pattern is present at the very earliest stage of stimulus processing (see above) and is seen in the CNS of anesthetized animals as well as awake animals that are licking (Nishijo and Norgren, 1991). The phasic portion of the response has been defined arbitrarily as the initial segment lasting between 0.3 s (Ganchrow and Erickson, 1970) and 2 s (Di Lorenzo and Schwartzbaum, 1982; Di Lorenzo and Victor, 2003) depending on the particular investigation. Some investigators have analyzed the phasic and tonic components of taste responses separately (Di Lorenzo and Schwartzbaum, 1982; Di Lorenzo and Victor, 2003; Nagai and Ueda, 1981), while others have excluded the phasic portion of the response from their analyses because of its high variability (Doetsch and Erickson, 1970; Ganchrow and Erickson, 1970). Because it is known that rats can make behavioral decisions about taste stimuli within the first 1 s of a response (Halpern, 1985; Halpern and Tapper, 1971; Scott, 1974), the phasic portion of the response is thought to contain all of the necessary information for taste discrimination. However, analyses of the first 0.5 s of response in the CT nerve in the rat have shown that the temporal pattern of response cannot distinguish among taste stimuli representative of the four basic taste qualities (Nagai and Ueda, 1981). In contrast, in a study of taste responses in the rat NTS, Di Lorenzo and Victor (2003) have shown that spike timing in the initial 2 s of response of about half of the responsive cells contains information which discriminates among the four basic taste qualities. In the rabbit PbN, though analyses of the time course in the initial 2 s of response could not unambiguously identify all four basic tastants, hedonic value did appear to be related

to time course in this response interval; specifically, a higher rate of acceleration in spike rate signaled positive hedonic tone (Di Lorenzo and Schwartzbaum, 1982).

Related to the coding of hedonics, several investigators have reported a relationship between the ratio of the phasic to tonic portions of the response as a marker of behavioral preference (Scott and Mark, 1987; Travers and Norgren, 1989; Verhagen et al., 2003), where preferred tastants evoked smaller phasic to tonic ratios than less preferred tastants. Changes in the phasic to tonic ratio of response rates within a taste response have been demonstrated to occur following experimental procedures that alter the hedonic value of a tastant. For example, Chang and Scott (1984) used a conditioned taste aversion paradigm to render a normally preferred solution of sodium saccharin (0.0025 M) aversive and recorded the responses to this solution and to other tastants in NTS cells before and after training. In conditioned rats, NTS responses to the saccharin solution showed a phasic peak in the first 100 ms of response that was not present in responses to saccharin in unconditioned rats. The addition of this peak to the saccharin response in the NTS of conditioned rats had the effect of increasing the phasic to tonic ratio (indicative of aversiveness) and causing the across-unit responses to saccharin and quinine to become more similar to each other than they are in the NTS of unconditioned rats. Conversely, Giza et al. (1997) conditioned rats to prefer one of two solutions; citric acid or $MgCl_2$ and showed changes in the temporal patterns of NTS responses following conditioning. The temporal responses to citric acid changed as a result of appetitive conditioning and became less similar to those of aversive taste stimuli. The phasic-to-tonic ratio in NTS responses to citric acid in conditioned rats was 1.2 (similar to that of glucose), while in controls it was 1.7, indicating a shift toward increased palatability as the stimulus became more acceptable following training. Scott and Mark (1987) have reported that this ratio varies between <1 for sugars, which are highly palatable, to >5 for highly unpalatable bitter stimuli.) For $MgCl_2$, although there was not a similar shift in the phasic-to-tonic ratio of the response in conditioned rats, responsiveness to $MgCl_2$ was lower in acid-best cells and the across unit pattern generated by $MgCl_2$ was more distinct from that generated by sour and bitter tastants. These data suggest that other mechanisms, perhaps in addition to the phasic-to-tonic ratio of a response, may be utilized to represent the hedonic value of a taste stimulus.

In addition to phasic-tonic responses, a second type of time course of response has also been described in the taste system. This type of response is characterized by rhythmic bursts of spikes with a periodicity ranging from 200–400 ms (Ogawa et al., 1973). The regularity and frequency of this rhythmicity increases with increasing concentration (Ogawa et al., 1974). Most reports of rhythmic responses associate this characteristic with sweet stimuli (Ogawa et al., 1974), though rhythmic responses have been reported to occur to a lesser degree (15% of the time or less) in

response to NaCl, HCl, quinine, and KCl (Nagai and Ueda, 1981). Rhythmic bursting responses have been described from periphery to cortex: in the CT (Mistretta, 1972; Nagai and Ueda, 1981; Ogawa et al., 1974), the NTS (Travers and Norgren, 1989), PbN (Scott and Perrotto, 1980), VPMpc (Scott and Erickson, 1971) and cortex (Yamamoto et al., 1984). However, Di Lorenzo and Victor (2003) failed to see this bursting response in taste cells in the NTS.

A third type of response pattern is one that gradually builds in magnitude (firing rate) over several seconds—a "buildup" pattern (Di Lorenzo and Schwartzbaum, 1982; Scott and Perrotto, 1980; Yamamoto et al., 1984). Scott and Perrotto (1980), for example, describe a slowly developing response to sucrose. Although this response occurs under normal testing conditions, it is not very common and it is unknown what information might be conveyed by cells that respond in this fashion.

Work of Katz et al. (2001, 2002a, b) has shown that the time course of response to taste stimuli in neurons in the gustatory cortex of awake, behaving rats can be used to identify taste stimuli. In fact, when taste-related differences in time course of response were considered in addition to changes in average response rate, the proportion of cells that could be identified as responding differentially to taste stimuli rose from 14.4% (13/90) using only average rate to 41% (37/90) when changes in time course were included. Furthermore, orderly changes in firing rate over the response interval that differed across stimuli in some cells resulted in changes in the identity of the best stimulus depending on the particular portion of the response that was examined. Moreover, Katz et al. (2001) showed that modulation of firing rate across the time course of cortical taste responses reflects the processing of different types of information: The time of occurrence within the response and the frequency of these rate modulations across taste responses is shown in Fig. 5. Results showed that the initial, somatosensory epoch (<0.2 s) was characterized by an equal cellular response to all tastants and water. The second, chemosensory epoch (0.2 to 1.0 s) was character-
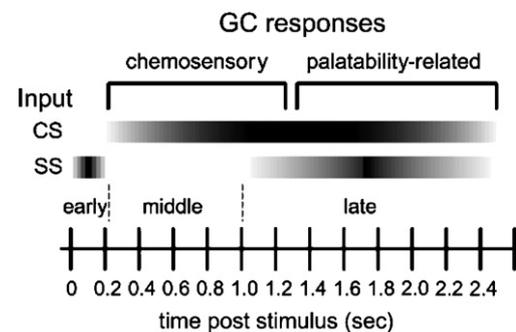

Fig. 5. A diagram of the response to taste stimuli in the gustatory cortex (GC) showing the division of the response into epochs where different types of information are presumably encoded. Abbreviations: CS, chemosensory; SS, somatosensory. Reprinted from Katz et al. (2002) by permission.

ized by a difference in response magnitude for the various taste stimuli that were tested. The third, hedonic epoch (> 1.0 s) was characterized by a high correlation between the similarity of responses between appetitive (sucrose and NaCl) or aversive (quinine and nicotine) stimuli.

In addition to differences in the time course of response, there are other aspects of the temporal structure of a response that convey information that might be used to discriminate among taste stimuli. For example, distinctive ISI distributions within a cell that vary across taste stimuli have been described in the CT nerve (Nagai and Ueda, 1981; Ogawa et al., 1974). However, these distributions were not the same for all cells. In the NTS, however, a given cell displayed similarly shaped ISIs across tastants (Nuding et al., 1991). On the other hand, fast Fourier transforms of recordings from the oral somatosensory and gustatory cortices showed that the somatosensory cortex activity was modulated at 5–10 Hz which corresponded to licking, but no such modulation was associated with taste response in the gustatory cortex (Katz et al., 2001).

7. Synchronous activity as a mechanism for temporal coding of taste

The occurrence of synchronous firing among neurons as they respond to a stimulus represents a potential mechanism of temporal coding in the taste system that has also been explored in recent years. As new methodologies are developed that allow multisite recordings and quantitative analyses of simultaneous firing among multiple cells, data have pointed to the idea that neuronal ensembles, grouped by their coherent firing, are capable of conveying information about taste stimuli whether or not they increase their firing rate in response to a taste stimulus (Katz et al., 2002a, b; Yokota et al., 1997, 2001; Nakamura and Ogawa, 1997).

Adachi et al. (1989) reported the results of an experiment designed to examine synchronous firing of taste-responsive cells in the rat NTS. Synchronous firing was measured using cross correlograms (CCGs, Perkel et al., 1967) of simultaneously recorded neurons during presentation of water or representatives of the four basic taste qualities. CCGs were calculated as the correlation coefficients of the two spike trains in response to each taste stimulus. Peaks in the CCG are indicative of an association of the timing and frequency of firing of one neuron in reference to the other (see Moore et al., 1970; Perkel et al., 1967). Three measures were derived from the taste responses and their associated CCGs: (1) The response density (RD) which was the mean response magnitude minus the firing rate during water presentation, (2) the frequency of correlated discharge (FC), which represented the degree to which a given tastant could drive a pair of neurons to fire in a correlated fashion, and (3) The weight of the correlated discharges (WC; WC = FC/RD), which conveyed the relative incidence of correlated discharge in the responses of the neuron pair. Eleven of 22 pairs of simultaneously recorded neurons

showed significant peaks in their CCGs. When present, correlated firing was most often observed to all effective tastants, defined as those tastants that evoked a response, although in some neuron pairs only a subset of effective tastants produced correlated discharges. Most pairs of neurons with correlated firing shared the same best stimulus (7 of 11 compared with 2/11 in the cross-correlation negative group), namely NaCl. Compared to NaCl responses where the FC values were high but WC values quite low, WC values were high in response to sucrose but FC values were low, suggesting that correlated firing among neurons plays a more significant role in encoding sucrose compared with other tastants, even though the response rate evoked by sucrose is often low.

A similar experiment was conducted by Yamada et al. (1990) on pairs of simultaneously recorded neurons in the rat PbN. Out of 23 pairs recorded, 11 had significant peaks in their cross-correlations. Nine of these 11 pairs shared the same best stimulus (eight pairs were NaCl best and the other pair was HCl best) while 5 of the 12 pairs with negative cross-correlations shared the same best stimulus (four pairs were NaCl best and the other pair was sucrose best). Several differences between the correlated pairs of neurons in the NTS and PbN were apparent. First, the peaks in the CCGs of correlated neuron pairs were much broader in the PbN than in the NTS. Fig. 6 shows CCGs for NaCl responses in the NTS and PbN that illustrate this point. Second, all neuron pairs with positive correlations in NTS had peaks in the CCGs associated with water; this was not the case for all neuron pairs in PbN. Third, FC and WC values during NaCl and HCl stimulation were much higher in PbN neuron pairs than in NTS neuron pairs, implying that more spikes were synchronized in PbN responses than in NTS responses, and that synchronized spikes comprised a larger proportion of the taste-evoked spikes in these responses. Based on these results, the authors argued that synchronous discharge among neurons may be a more prominent coding mechanism in the PbN than in the NTS.

Peaks in the CCGs associated with water were interpreted by both Adachi et al. (1989) and Yamada et al. (1990) to be the result of somatosensory input converging on taste-sensitive neurons in the brain stem. These authors suggested that these data are consistent with the finding that tactile and taste inputs converge onto cells in the taste-responsive nuclei of the brain stem (Ogawa et al., 1984). Furthermore, they suggested that convergent gustatory and tactile input enhances synchrony among cells in these areas. As discussed above, Katz et al. (2001, 2002a, b) reported that somatosensory input evokes the very earliest (< 0.2 s) portions of the neocortical response to taste while purely chemosensory input evokes the response that occurs in the interval between 0.2–1.0 s. While it is not known whether a similar parsing of influences occurs in the brain stem, the observation that taste identification may be made within approximately 200 ms (Halpern and Tapper, 1971) indicates that chemosensory information (perhaps in
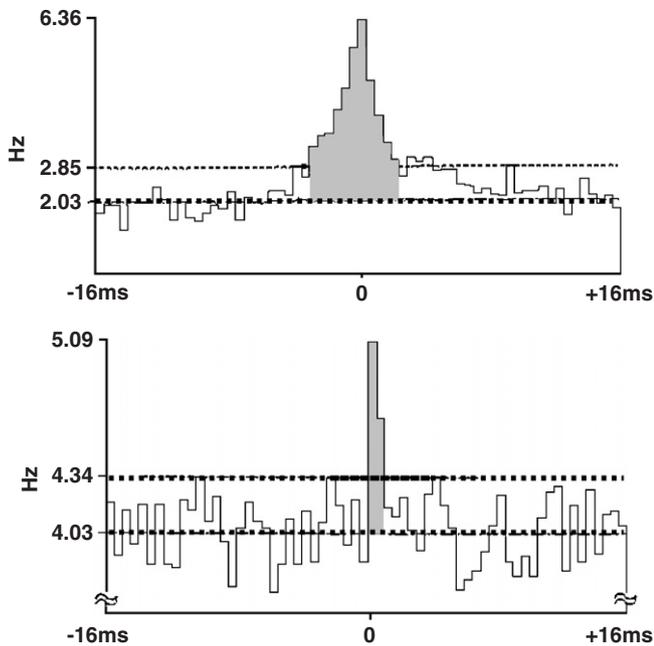
Fig. 6. Examples of CCGs associated with responses to NaCl in the NTS (top, from Adachi et al., 1989) and the PbN (bottom, from Yamada et al., 1990) showing a wider peak in the NTS compared with the PbN. Shaded area in each panel indicates the portion of the CCG that was used to calculate the weight of the correlated discharge (see text for details). Dashed lines indicate the largest bin that is not part of the peak and the mean value of the bins that are not part of the peak, respectively. Adapted from Adachi et al. (1989) and Yamada et al. (1990) by permission.

addition to tactile information) must be contained in the earliest portions of responses to taste stimuli in the brain stem, and that this information may be sufficient for behavioral taste discrimination (Spector, 2000). Katz et al. (2001, 2002a, b) point out that, in the cortical taste areas, the processing of taste stimuli may continue even after taste quality has been identified.

The observation that CCGs of simultaneously-recorded neurons in the PbN showed wider peaks (3–8 ms) than those in the NTS (<1.5 ms) (Adachi et al., 1989) was interpreted by Yamada et al. (1990) to suggest that the coherence of PbN neuron pairs is influenced by feedback from higher gustatory structures. Consistent with these findings are analyses of simultaneously recorded NTS-PbN neuron pairs (Di Lorenzo and Monroe, 1997). These data show that the temporal pattern of response in the PbN is correlated with that in the NTS only in the initial response interval (<500 ms), suggesting that the later portions of PbN responses may be determined by input from other sources, either intrinsic or extrinsic in origin. Yokota et al. (1996) reported that CCGs of neuron pairs in the gustatory cortex also have wider peaks (~8 ms) than those in the NTS. They interpreted this result as reflecting differences in firing rates in the cortex vs. the brain stem and argued that synchrony among neurons may be more prominent in the brain stem than the cortex. On the other hand, Katz et al. (2002a, b) showed that coherence among ensembles of

taste-responsive neurons in the cortex can occur over much longer timescales (ca. hundreds of msec) than at the brain stem level (up to 10 ms; Yamada et al., 1990), providing the opportunity for input from multiple sources to shape the temporal structure of these responses. As Katz et al. (2002a, b) have argued, evidence is mounting that processing of taste stimuli in the brain is accomplished by an interrelated and widely distributed network of neurons.

Studies of correlated neuron pairs in the gustatory neocortex have underscored the idea that synchronous firing among neurons, even in the absence of increases in firing rate, represents a potential coding mechanism for taste stimuli (Katz et al., 2001; Katz et al., 2002a,b; Nakamura and Ogawa 1997; Yokota et al., 1997, 2001). Among those pairs of cells that do show taste-related increases in firing rate, the prominence of correlated discharges is greater among cells that share the same best stimulus (Yokota and Satoh, 2001). Furthermore, groups of cells with the same best stimulus, and that show the strongest tendency to fire synchronously, are located closer together in the cortex than those with disparate best stimuli and dissimilar response profiles (Nakamura and Ogawa, 1997; Yokota and Satoh, 2001). These findings suggest that cortical organization of gustatory sensitivities may reflect the spatial segregation of responsiveness to different tastants, that is, a chemotopic map.

8. Mechanisms for reading temporal codes in the gustatory system

Whatever the evidence that a particular type of code is present in the nervous system, there always remains the question of whether this information is actually used. One approach is to correlate analyses of physiological data with behavioral performance. For example, evidence supporting the across neuron pattern theory was provided by Scott (1974) by correlating the behavioral patterns of cross generalization of a conditioned taste aversion with the similarity of across neuron patterns of response in the NTS. Similarly, data consistent with the labeled line theory were provided by both neurophysiological and behavioral studies using amiloride, a NaCl channel blocker. Since it is known that one of the major transduction pathways for NaCl involves entry of NaCl through apical Na channels, blocking those channels provides a paradigm for specifically attenuating the perception of saltiness. Accordingly, the disruption of behavioral discrimination between NaCl and KCl that follows amiloride administration (Spector et al., 1996) has been correlated with a specific decrease in the response to NaCl in NaCl best cells in the NTS (St. John and Smith, 2000). The NaCl response in other cells (i.e. cells in other best stimulus categories) may not be as affected by amiloride because these cells may receive information about NaCl through the activation of transduction mechanisms that are not amiloride-sensitive. The fact that amiloride suppresses the distinctiveness of NaCl and suppresses the NaCl response only (or mostly) in NaCl

best cells suggests that NaCl best cells are a unique cell type that is responsible for the neural representation of saltiness. NaCl best cells, then, would presumably constitute a labeled line. In the case of temporal coding, the challenge is to show that information contained solely in the temporal arrangement of spikes is meaningful, that is behaviorally relevant, in spite of the possibility that not all cells utilize a temporal code (Bradley et al., 1983; Di Lorenzo and Victor, 2003; Nagai and Ueda, 1981) and further, that each cell may utilize its own unique temporal code.

In our work, we have made certain assumptions about these issues in order to investigate the utility of temporal coding. In particular, we have assumed that the temporal code for taste, if there is one, is contained in the temporal pattern of spike trains of taste responses in individual cells, not in the systematic changes in the firing rate over time across cells. Moreover, we have assumed that driving all the elements in a taste-related area with this temporal pattern will stimulate the critical elements (along with others) that can interpret the information; essentially, we assume that there is some relationship, albeit undefined at this time, between a temporal code at the level of a single unit response and a temporal code at the level of the population response. With these assumptions in mind, we have adapted a technique first used by Covey (1980) in her dissertation. Covey patterned electrical pulse trains after the temporal arrangement of spikes in taste responses recorded from the NTS. To test whether the temporal information contained in the spike train was meaningful, these patterned pulse trains were used to stimulate the CT nerve in awake decerebrate rats. Orofacial reactions to this type of electrical stimulation were identical to those evoked by the corresponding natural taste stimuli.

In our investigations, we have also used electrical pulse trains that were based on the responses to natural tastes; however we delivered these pulse trains to the NTS in intact, behaving rats, and tested the extent to which this stimulation was similar to a natural taste sensation. Our hypothesis was that if the temporal pattern of activity in a taste response were played back into the system, it would evoke a taste-like sensation of predictable quality and hedonic value. Accordingly, we constructed pulse trains that were based on the temporal pattern of spikes evoked by single cells in the NTS in response to sucrose and quinine in a previous experiment (Di Lorenzo et al., 1986). Fig. 7 shows the spike trains that were used and the temporal arrangement of electrical pulse trains that were used to simulate these responses.

Our first goal was to show that rats could learn to avoid lick-contingent NTS stimulation when it was paired with an i.p. injection of LiCl in a conditioned taste aversion paradigm (Di Lorenzo and Hecht, 1993). In this study, a lick of water was followed by a 1 s electrical pulse train in which the temporal arrangement of pulses mimicked the sucrose response of an NTS neuron (called a sucrose simulation pattern, see Fig. 7). When the temporal pattern of electrical stimulation was changed from one that mimicked sucrose to one that mimicked quinine (called a quinine simulation pattern), rats avoided licking without any conditioned aversion training.

Our most recent set of experiments supported and extended our previous findings (Di Lorenzo et al., 2003). In the first experiment, licking of water was suppressed when the lick-contingent pulse trains were based on two different single cell responses to quinine, but not when the interpulse intervals contained in the pulse trains were randomly shuffled. Fig. 8, top, shows the results of this experiment. In a second experiment, rats avoided lick-contingent electrical stimulation of the NTS that mimicked the temporal pattern of a sucrose response following stimulation-illness pairings. This aversion generalized to natural sucrose but not to NaCl, HCl or quinine; extinction of the aversion to electrical stimulation also extinguished the aversion to sucrose. Fig. 8, bottom, shows these data.

Collectively, these results imply that the temporal sequence of electrical stimulation of the NTS may convey
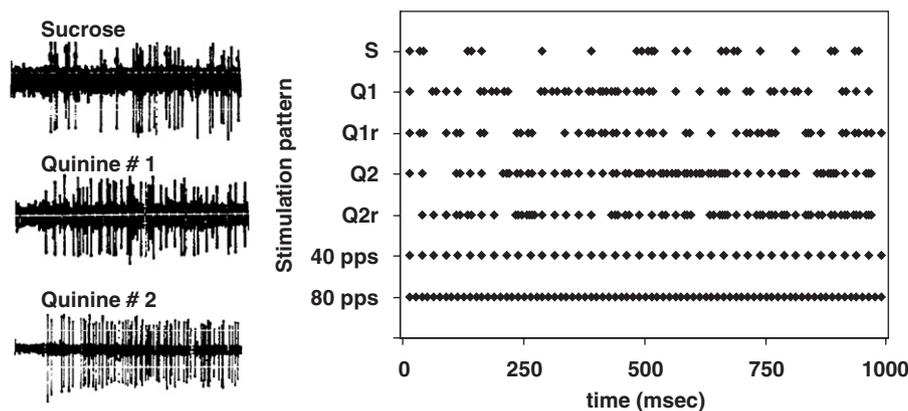

Fig. 7. Left panel shows oscilloscope tracings of responses to sucrose and quinine recorded in the NTS of anesthetized rats (from DiLorenzo et al., 1986). The temporal patterns of spikes in these responses were used to construct the electrical pulse trains used in Di Lorenzo and Hecht (1993) and in Di Lorenzo et al. (2003). Right panel shows the pattern of electrical pulse trains over a 1 sec interval. Diamond shapes indicate individual pulses. S = sucrose simulation pattern; Q1 and Q2 = quinine simulation patterns; Q1r and Q2r = the quinine simulation patterns in which interpulse intervals are randomly shuffled; pps = pulses per second. Reprinted from Di Lorenzo et al. (2003) by permission.

meaningful, i.e. behaviorally interpretable, information, and that electrical stimulation that mimics typical temporal patterns of response to specific taste stimuli provides the critical neural elements in the NTS or its target structures with the precise sequence required to elicit a behavioral response. For example, different groups of NTS cells, perhaps defined by their best stimulus or by their target of projection, might be preferentially responsive to various interspike intervals contained in their input. Extrapolated across the population of NTS cells, it is possible that afferent volleys with different temporal patterns might maximally excite different groups of cells. This would provide a mechanism whereby temporally encoded information would be transformed into a spatial code. This sort of spatiotemporal distribution of activity might then be used to segregate afferent signals to initiate appropriate motor reflexes. It also seems likely that the electrical stimulation may have evoked synchronous (or near synchronous) firing in multiple units, suggesting that cooperative activity among NTS cells may be important for the reported effects. Dynamic ensembles of neurons, all

firing in synchrony, might provide a more effective input to target structures than an asynchronous volley from the same groups of cells. Whether and how the neural structures that receive projections from the NTS process the temporal structure of this input is unknown but may be a fruitful area of future investigation.

9. Summary and conclusions

Early investigations of temporal coding in the gustatory system concluded that the time course of responses in some neurons showed systematic differences across the various classes of taste stimuli, implying that temporal parameters other than overall firing rate can convey information about a taste stimulus.

More recent investigations of neural coding in sensory systems have focused on time-dependent patterns of the neural response, i.e. temporal coding, as a mechanism of communication in neural circuits. Studies of temporal coding in the gustatory system have grappled with several unique methodological challenges, including the quantitative description and comparison of temporal patterns as well as the assessment of the relative contributions of spatial and temporal coding to the information contained in a response. Other investigations have suggested that the cooperative activity among synchronously firing ensembles of taste-responsive neurons at all levels of processing in the brain can convey information about taste quality. Behavioral studies using patterned electrical stimulation of the brain in awake animals have supported the idea that temporal coding of taste stimuli may have functional significance. Investigations of temporal coding in the taste system can be expected to become more numerous as new technologies and approaches enable the quantitative assessment of changes in responses over time and space as a conveyor of information.
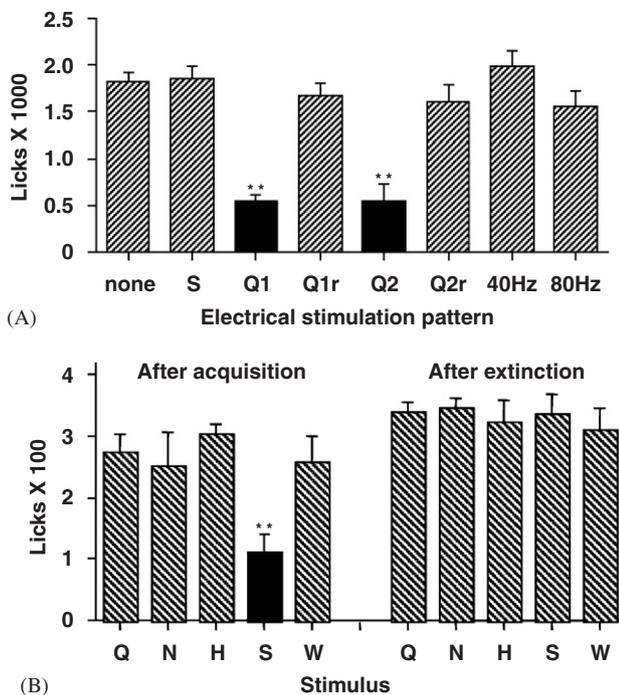
Fig. 8. (A) Mean ($\pm$SEM) number of licks with various temporal patterns of electrical stimulation of the nucleus of the solitary tract in 10-min sessions. S = sucrose simulation pattern; Q1 and Q2 = quinine simulation patterns based on electrophysiological responses of two different NTS cells to quinine; Q1r and Q2r = the quinine simulation patterns in which interpulse intervals are randomly shuffled. $**p<0.01$. (B) Mean ($\pm$SEM) number of licks to 1-min presentations of natural taste stimuli following acquisition of a conditioned aversion to the sucrose simulation pattern of electrical stimulation and following extinction. Experimental rats ($n = 7$); histological controls ($n = 4$). Q = quinine; N = NaCl; H = HCl; S = sucrose; W = water. Asterisks denote a statistically significant difference ($p<.01$) between the number of licks for sucrose after acquisition and the number of licks for sucrose after extinction in the experimental group. Adapted from Di Lorenzo et al. (2003) by permission.

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