Feature Article
The Structure and Function of Dynamic Cortical and Thalamic Receptive Fields

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Under natural conditions, animals must process spatiotemporally complex signals in order to guide adaptive behavior. It follows that the response properties of neurons should reflect the dynamic nature of such signals. Recently, several studies have demonstrated the existence of time-varying receptive fields in the auditory, visual and somatosensory thalamocortical pathways. The characteristics of these receptive fields suggest that they are constrained by the need to actively interpret time-varying stimuli. Here, we review these studies, the possible functions of these receptive fields, and how they might be generated in the thalamocortical pathway.

The Time-dependence of Sensory Processing

Sensory signals in the natural environment typically have intricate time-varying properties. Responding to vocalizations, tracking predators, and foraging all involve complex, time varying sensory signals. Animals can perceive such sensory stimuli very rapidly and adjust their behavior accordingly. Furthermore, when animals engage in exploratory behaviors, they do so by moving their sensory receptor arrays. During haptic exploration, primates (including humans) employ stereotypical movements of their hands to optimally perceive tactual differences in object size, texture and shape (Darian-Smith, 1984). Analogous dependencies between active exploration and optimal sensory discrimination have been observed in other sensory modalities, such as saccadic eye movements during visual search and object recognition and head orientation movements for sound localization and recognition. Thus, most of the sensory information gleaned from the environment is sampled through actions and unfolds continuously over a time-scale of milliseconds to seconds.

The nervous system must be able to integrate such signals in an efficient manner and the responses of neurons should reflect the time-varying nature of sensory inputs. Here, we review the existence and structure of time-varying receptive fields (RFs) in the thalamocortical pathway of the mammalian auditory, visual and somatosensory systems, how they might be generated and how these RFs may allow thalamocortical neurons to integrate time-varying sensory signals. Throughout this review, we will use the word 'dynamic' to refer solely to the spatial (or spectral) properties of RFs that change on a millisecond time-scale.

Mapping Receptive Fields in Space and Time

Since the early work in the visual system (Hartline, 1940), the analysis of the RF properties of single neurons has occupied center stage in sensory neurophysiology. Generically speaking, the RF of a neuron is defined as the area of a particular 'parameter space' within which a stimulus can elicit a neuronal response (measured in spike counts or the average firing rate) that is significantly above or below the spontaneous firing rate. Spatial coordinates (for the visual and somatosensory system), spectral coordinates (in the case of the auditory system), or an arbitrary parameter space that has behavioral relevance (such as a set of odors or tastants for the olfactory and gustatory systems) are examples of possible parameter spaces. Using this approach, systems neuroscience has made enormous strides in discovering the functional organization of the brain and the response properties of neurons within cortical areas and thalamic nuclei. Nevertheless, the time-varying properties of thalamocortical RFs have not been thoroughly explored until recently.

The development and application of alternative RF mapping techniques has facilitated the characterization of RFs in both the spatial and temporal domains. In general, two approaches have been used extensively: the response-plane and reverse-correlation techniques. In the response-plane method (Gerstein *et al.*, 1968), the response profile of a neuron to a set of stimuli is examined across post-stimulus time (Stevens and Gerstein, 1976; Palmer and Davis, 1981; Dinse *et al.*, 1991; Nicolelis and Chapin, 1994). By comparing the stimulus that elicits the strongest response from a neuron at one post-stimulus time with the stimulus that elicits the strongest response at a later time, it is possible to examine how the RF structure of a neuron changes on a millisecond time-scale.

In the reverse correlation method – a technique pioneered by de Boer (de Boer and de Jongh, 1978) – a neuron's response is reconstructed according to the stimulus sequence. For each spike of a given neuron's response to the stimulus sequence, this method reconstructs the exact stimulus delivered preceding it. In other words, the occurrence of a spike is an indication that something particular happened within the stimulus sequence preceding the spike. Each spike is considered a potential indicator for a stimulus that could drive the neuron. For this type of approach, the set of stimuli can be quite diverse, ranging from white noise to a discrete set of pre-selected stimuli. By correlating the spike times with the stimulus in a given time interval prior to the spike, one can obtain an estimate of the average stimulus that caused the spikes. Because this procedure identifies the stimulus as a function of time before the spikes occurs, it is called reverse-correlation. Application of either the response-plane or the reverse-correlation methods in different sensory systems has demonstrated the existence of time-varying RFs across the thalamocortical pathway of different sensory systems.

It is important to note, however, that an underlying assumption in the interpretation of dynamic RF data is that the structure characterized by these methods allows one to predict the response to a novel time-varying stimulus that was not used in the initial RF characterization. Thus, there is an assumption of linearity that may or may not be valid depending on the neural structure and the stimuli used (Theunissen *et al.*, 2000).

Time-varying Frequency Tuning of Auditory Cortical Neurons
Information embedded in the form of duration, intervals and

temporal order of acoustic stimuli are important parameters for auditory signal processing in many species. Several elegant studies have established that different nervous systems use a variety of temporal cues (i.e. inter-aural time differences, duration, inter-syllable intervals, etc.) to process auditory signals which guide adaptive behaviors (Hauser, 1996). It has, therefore, been suggested that the characterization of auditory neurons is best accomplished by combining the spectral and temporal features, as compared to mapping frequency sensitivity and temporal response properties separately (Eggermont et al., 1981).

The spectrotemporal RF of an auditory neuron represents the specific characteristics of a sound stimulus in both the time and frequency domain that affect the firing probability of the neuron. In mammals, the classical example of time-varying auditory RFs has been the echo delay tuned neurons of the bat (Suga et al., 1983). For example, the mustached bat (Pteronotus parnellii) emits a vocal signal, called a 'pulse', which has two components: a long duration constant frequency component and a shorter duration frequency modulated component. The timing between the emitted pulses and their echoes and the changes in frequency and amplitude in echoes caused by prey are used to detect target identity and target range. The different attributes of the frequency modulated and constant frequency components have led to a corresponding functional differentiation of the auditory cortex of this species (Fitzpatrick et al., 1998). Receptive fields in the bat auditory cortex respond to the frequency range of one component of the emitted pulse and also to the frequency range of the echo. Sensitivity to either of these frequency ranges is time-dependent. Put another way, bat auditory cortical neurons respond best to one frequency at one time, and then to another frequency after a particular time delay. The frequency and time delays correspond to the species-specific vocal signals used for echolocation of prey and/or communication among conspecifics (Suga et al., 1987; Kanwal, 1999). While bats may be specialized for the use of echolocation, they are not the only mammals that need to process time-varying ethologically relevant signals. Thus, it is unlikely that they are the sole mammalian species with time-varying auditory neurons.

Beyond bats, very few neurophysiological studies have systematically addressed how the spectrotemporal information embedded in complex sounds may be reflected in the RFs of neurons in the mammalian auditory system. In the cat auditory cortex, neurons may show excitatory responses to more than one frequency range, and these ranges may be separated by ranges of no excitation or inhibition (Oonishi and Katsuki, 1965; Abeles and Goldstein, 1972). Sutter and Schreiner (Sutter and Schreiner, 1991) studied the distribution of these neurons with 'multi-peaked' tuning curves in depth. By presenting acoustic stimuli of 675 different frequency-level combinations to each neuron in a pseudo-random order, neural responses were constructed using an approach similar to the response-plane method. In this manner, a class of neurons was found in the dorsal part of primary auditory (A1) cortex that, like those described previously (Oonishi and Katsuki, 1965; Abeles and Goldstein, 1972), exhibited two to three separate excitatory frequency ranges. These investigators also showed that the responses to different frequency ranges occurred at different latencies (Sutter and Schreiner, 1991). The lowest frequency stimulus most often induced the shortest latency neuronal response while the highest frequency stimulus led to the longest latency responses. Thus, these auditory cortical neurons seem to exhibit what one would consider a spectrotemporal RF; their frequency tuning changed as a function of post-stimulus time. As

Sutter and Schreiner (Sutter and Schreiner, 1991) suggest, such neurons could conceivably be used to encode conspecific vocalizations (Shipley et al., 1991) or the vocalizations of their prey (Ehret, 1980).

In primates, deCharms and colleagues (deCharms et al., 1998) recently described the existence of spectrotemporal RFs in A1 cortex of the awake owl monkey (Aotus trivirgatus). Here, the auditory stimuli consisted of rapid sequences of tones or chords, and the reverse-correlation method was used to relate neuronal firing patterns with these sound sequences. As mentioned above for cats, most neurons in the owl monkey A1 cortex have RFs whose best-frequency varies as a function of time (deCharms et al., 1998). The majority of A1 neurons had complex RFs that included regions of both excitation and inhibition, as well as time-varying frequency tuning. For example, some neurons had narrow regions of excitation flanked by inhibitory regions above (i.e. at a relatively higher frequency range) and below it (i.e. at a relatively lower frequency range). Other neurons had excitatory or inhibitory responses to one frequency range at one time and another frequency range at a later time. Figure 1A shows an example of a spectrotemporal RF of an A1 neuron recorded in the awake owl monkey. This neuron had a complex RF structure with multiple excitatory and inhibitory subregions. It is also evident that the preferred frequencies for excitation and inhibition change as a function of time. Tramo and Cariani (Tramo and Cariani, 1999) reported similar spectrotemporal RFs for auditory cortical neurons in the awake rhesus monkey (Macaca mulatta).

DeCharms et al. (deCharms et al., 1998) suggested that the spectrotemporal RFs of owl monkey auditory neurons may indicate preferences for stimulus edges, stimulus transitions in frequency or intensity, and conjunctions of different stimulus features. In order to test this hypothesis, the RFs of auditory cortical neurons were used as guides in the construction of stimuli. When matched to their appropriate spectrotemporal RF, such stimuli elicited robust responses from auditory cortical neurons (deCharms et al., 1998). Stimuli which deviated spectrally or temporally from the RF elicited weaker responses. Thus, these authors concluded that neurons in A1 of the owl monkey could exhibit 'combination selectivity' to tone stimuli.

Brosch and colleagues (Brosch et al., 1999) investigated the relationship between combination sensitivity and the spectro-temporal tuning properties of cortical neurons in A1 and the caudomedial area of macaque auditory cortex using two-tone sequences. By holding the frequency of the second tone constant and varying the frequency and onset time of a preceding first tone (the 'stimulus onset asynchrony'), they found that ~60% of multi- and single-units showed response enhancement to sequences of two tones. That is, compared with presenting the second tone in isolation, the response to the two tones in succession elicited a significantly enhanced response. While such response enhancement occurred for a variety of tone frequencies and a wide range of inter-tone intervals, a given neuron often exhibited a unique and restricted spectrotemporal response profile. In other words, a given neuron fired best to a two-tone sequence if each of the tones were within a specific frequency range (which could be different for each tone) and separated by a specific inter-tone time interval. Figure 1B shows an example of the spectrotemporal response area of a multi-unit group relative to the second tone. In this particular case, the second tone is 8 kHz. The magnitude of the response enhancement is indicated in the color scale. For this multi-unit
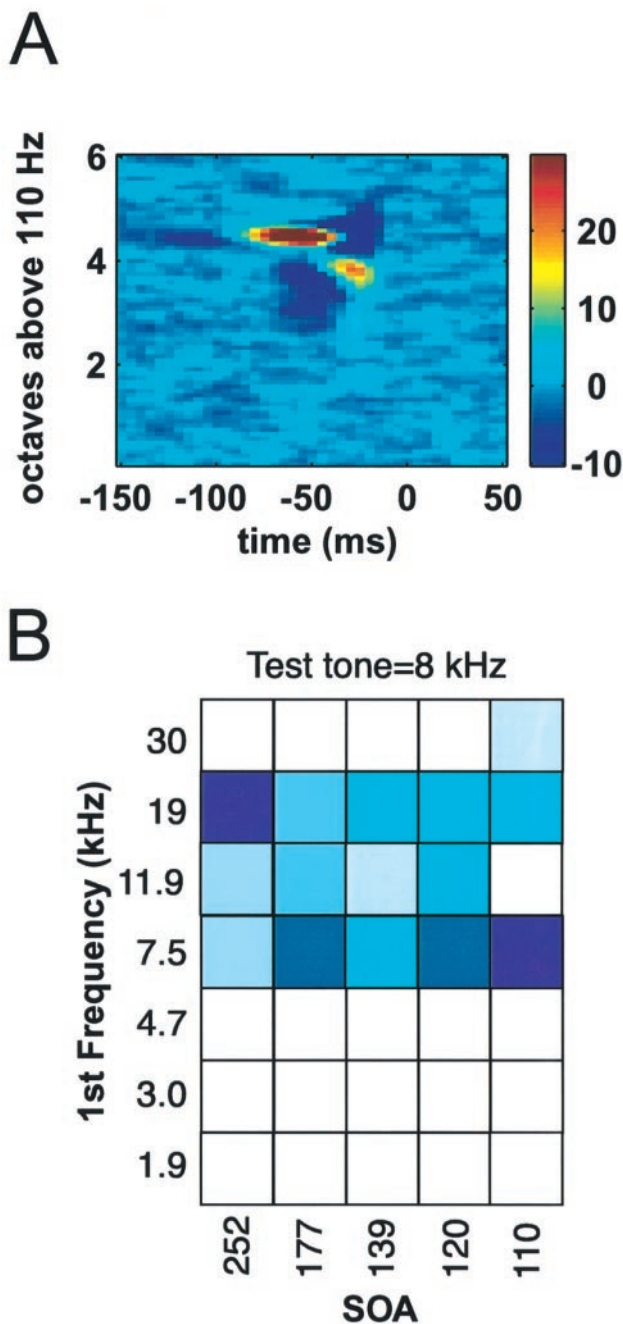
Figure 1. (*A*) Spectrotemporal receptive field of a neuron in the primary auditory cortex of an awake owl monkey (*Aotus trivirgatus*). Receptive field structure corresponds to the average spike rate (color bar on right) from the neuron recorded at time zero by each stimulus component frequency at the time lag shown on the *x*-axis. The *y*-axis corresponds to the frequency of the stimulus; the scale is in terms of 'Octaves above 110 Hz'. [Figure reprinted with permission from Decharms *et al.* (Decharms *et al.*, 1998).] (*B*) Spectral and temporal dependence of response enhancement in single neuron recorded from the auditory cortex of a ketamine-anesthetized macaque monkey (*Macaca fascicularis*). Each box displays the magnitude of response enhancement that was observed during the presentation of a test tone (always 8 kHz) that occurred after presentation of another tone (frequency indicated on the *y*-axis) at different intervals between the onsets of the two tones (stimulus onset asynchrony, SOA) indicated on the *x*-axis. Magnitude of response enhancement for each frequency/SOA combination is proportional to the blue shading (dark blue represents the strongest enhancement, white represents no enhancement). [Figure redrawn from Brosch *et al.* (Brosch *et al.*, 1999).]

group, the degree of combination sensitivity is directly related to both the spectral and temporal features of the tone sequence.

Although much work is needed in relating the spectrotemporal properties of auditory neurons to stimulus preferences, the results described here suggest a mechanism for complex sound integration: the spectrotemporal RF of a neuron is directly related to its stimulus preference and will respond non-linearly to such stimuli when compared to isolated components of the stimulus. In frogs and birds, the spectrotemporal RFs of auditory neurons have been related to the responses of the same neurons to species-specific vocalizations (Eggermont *et al.*, 1983; Theunissen *et al.*, 2000). These studies have found that the spectrotemporal RF can be used to predict neuronal responses to vocalizations to some extent.

What are such neurons for in cats and primates? Neuroethological work conducted in bats and birds suggests that such neurons may be used to integrate temporally complex, species-specific vocalizations (Suga *et al.*, 1983; Margoliash and Fortune, 1992; Kanwal, 1999). For example, neurons in both the bat auditory cortex and songbird forebrain display combination-sensitivity to conspecific calls or vocalizations, responding supralinearly to combinations of call elements when compared to call elements presented in isolation. Thus, the spectrotemporal RFs reported in cats and primates may similarly be involved in the integration of complex species-specific vocalizations. Such combination- and temporal-sensitivity in response to species-specific calls has been reported for auditory cortical neurons in the squirrel monkey (Bieser, 1998), marmosets (Wang *et al.*, 1995b) and in the rhesus monkey (Rauschecker *et al.*, 1995). However, there are large gaps in our knowledge of the relationship between the spectrotemporal RFs of primate auditory neurons, their responses and selectivity to vocal signals, and the relationship of their neural responses to behavior [for a review, see Ghazanfar and Hauser (Ghazanfar and Hauser, 1999)].

Time-varying Spatial- and Feature-tuning in the Visual System

Lateral Geniculate Nucleus

Like the RFs of retinal neurons, lateral geniculate nucleus (LGN) neuronal RFs can be described in purely spatial terms with an 'on-center', which responds to the onset of a bright stimulus, and an 'off-surround', which responds to the onset of a dark stimulus (or the off-set of a bright stimulus). Retinal and LGN neurons of the opposite polarity also exist. Stevens and Gerstein (Stevens and Gerstein, 1976) conducted one of the earliest studies that suggested time was an important dimension in the structure of LGN RFs. To characterize the RF of LGN neurons, these authors used the response-plane technique where the visually responsive area of a neuron was divided into a matrix. Neural responses were elicited using a brief flash of light and measured at each position in the matrix. Using this approach, the spatial description of cat LGN RFs, such as 'on–off' and 'center–surround', was insufficient to describe completely even the simplest of LGN RFs. Two different types of LGN RFs were revealed. One type displayed excitatory and inhibitory domains which remained stable over time, and another type exhibited excitatory and inhibitory domains which shifted as a function of post-stimulus time.

More recent experiments using reverse-correlation methods have supported the original results of Stevens and Gerstein (Dawis *et al.*, 1984; Reid and Shapley, 1992; Eckhorn *et al.*, 1993; Golomb *et al.*, 1994; Cai *et al.*, 1997; Reid *et al.*, 1997). In cats, for example, ON-center LGN neurons will often have a surround response that is delayed relative to the OFF-center response (Reid
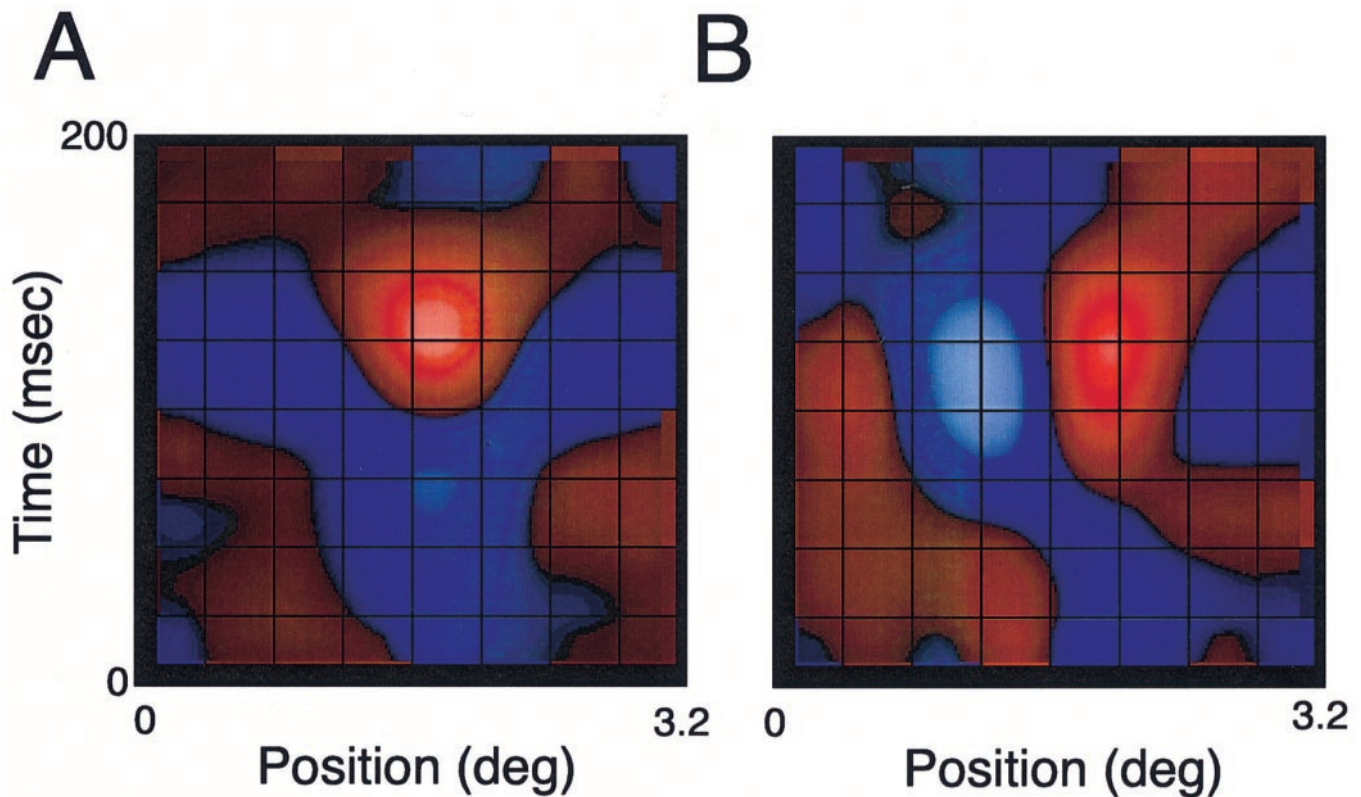
Figure 2. Spatiotemporal receptive fields of two neurons from the cat visual pathway. In these plots, time is represented by the *y*-axis and space on the *y*-axis (summed over the vertical dimension). Each pixel represents 25 ms and 0.4° of visual space. Red corresponds to 'on-responses', and blue corresponds to 'off-responses'. Brightness codes for response strength. (*A*) A neuron from the lateral geniculate nucleus. Note that the off-response is delayed relative to the on-response. (*B*) A simple cell from the striate cortex. The RF of this neuron is space-time inseparable and likely correlates with the neuron's directional selectivity. (Both panels courtesy of R.C. Reid, J.-M. Alonso and E.M. Usrey.)

and Shapley, 1992; Cai *et al.*, 1997) (Fig. 2*A*). Similar effects are seen in the retinal ganglion cells of the cat (Citron *et al.*, 1981). In the primate LGN, Golomb *et al.* (Golomb *et al.*, 1994) found that both parvocellular and magnocellular neurons had spatiotemporal RFs similar to those found in the cat LGN — the response to the surround was delayed relative to the response of the center.

Primary Visual Cortex

Receptive field mapping in both space and time has shown that V1 neurons respond to flashes of light in different subregions of their RFs at different times. In the cat primary visual cortex, many studies (using a variety of approaches) have demonstrated that the RF structure is space-time inseparable (Movshon *et al.*, 1978; Palmer and Davis, 1981; McLean and Palmer, 1989; Dinse *et al.*, 1991; Reid *et al.*, 1991; DeAngelis *et al.*, 1993; McLean *et al.*, 1994). In general, the RFs of simple cells in the cat visual cortex show a temporal evolution of their response patterns, whereby different response areas show different time courses. More specifically, particular spatial locations in the RF cannot be designated as ON or OFF subregions unambiguously because these regions seem to shift over time or overlap (Reid *et al.*, 1991; DeAngelis *et al.*, 1993). Furthermore, these temporally shifting regions are often 'oriented'. Figure 2*B* shows an example of a simple cell from the cat visual cortex which has a space-time inseparable RF.

One function of simple cell spatiotemporal RFs appears to be to establish the directional selectivity in these neurons (Reid *et al.*, 1991; McLean *et al.*, 1994). For example, Reid *et al.* (Reid *et al.*, 1991) measured the spatiotemporal RFs of simple cells in the cat using stationary gratings undergoing contrast reversal (Movshon *et al.*, 1978). They compared these response profiles with the directional selectivity of neurons as measured by drifting gratings. The authors found that the directional selectivity of neurons could, to some extent, be predicted by the linear summation of responses of stimuli moving across the spatiotemporal RF. Selectivity for the speed of moving stimuli can also be predicted from the spatiotemporal RFs of simple cells (McLean and Palmer, 1989).

In addition to the time-dependent organization of ON–OFF responses, other more complex properties of visual cortical neurons, such as their feature selectivity, also display time-dependent evolution on a millisecond scale. For example, orientation tuning, defined as the selectivity of neuronal responses to bars of light in a particular orientation, and length-tuning, the selectivity to bars of light of a particular length, have both been shown to be time-varying. Early evidence for time-dependence for the selectivity of these features was provided by Dinse *et al.* (Dinse *et al.*, 1991), who employed flickering bars of light of different lengths and the response-plane technique to investigate the time course of orientation tuning and length tuning in cat visual cortical neurons. These authors demonstrated, for both orientation and length tuning, that some neurons first exhibited a state of excitation that did not show selectivity, followed by the gradual sharpening of their selectivity over time. Other neurons showed selectivity for a particular orientation or length that remained stable over time, while for yet another group of neurons, the selectivity changed

over time (e.g. responding best to one orientation at one time epoch, and another orientation at a later time epoch).

In the primate visual cortex, a laminar comparison of dynamic orientation tuning of cells in V1 was performed by applying the reverse-correlation technique (Ringach *et al.*, 1997). These authors found that orientation selectivity developed over the first 30–45 ms of a response, and persisted for up to 85 ms. Comparing the nature of orientation selectivity across different layers of macaque V1, these authors observed that the degree of dynamic orientation tuning depended on the laminar position of the neurons. The cortical layers which received direct input from the LGN (layers 4Ca and 4Cb) contained neurons which showed a single, broadly tuned orientation preference that did not change over time, while neurons in the output layers of V1 (layers 2, 3, 4B, 5 and 6) showed a range of dynamic behaviors. In these 'output' layers, orientation tuning was narrower than neurons of the input layers, and their preferred orientations changed over post-stimulus time. Furthermore, as reported by Dinse *et al.* (Dinse *et al.*, 1991) for cat visual cortex, a subset of neurons in macaque V1 showed orientation tuning that increased in sharpness over time (Ringach *et al.*, 1997).

Similarly, for chromatic tuning, Cottaris and De Valois (Cottaris and De Valois, 1998) showed that the color RFs of macaque V1 neurons are also modulated over time. In these experiments, the stimuli consisted of rectangles whose colors varied randomly as a function of time. Using the reverse-correlation approach, the color tuning of V1 neurons in the anesthetized macaque varied over time and was not just a simple relay of color information from the LGN, and the time course suggests that corticocortical interactions may be involved. They also found different types of chromatic RFs: single-peaked RFs, double-peaked RFs, and RFs in which the color preference continuously shifted as a function of time (Cottaris and De Valois, 1998).

Dynamic Receptive Fields beyond the Primary Visual Pathway

In the visual system studies described above, RFs were mapped while the animal was anesthetized or, if it was awake, fixating on a point in visual space. Since in the real world, primates, for example, make saccadic eye movements to analyse visual scenes, it would be interesting to know the relationship between the active movements of the eyes and visual neurons' RF properties. Recently, Tolias and colleagues (Tolias *et al.*, 1997) conducted a study to investigate if and how the RFs of neurons in macaque V4 (a higher-order visual area) change in relation to saccadic eye movements. V4 neuronal RFs were mapped in the following way. The subject began the trial by fixating on a spot and a probe stimulus then appeared and remained for the duration of the trial. Following the appearance of the probe, a visual target was displayed to which the subject had to saccade in order to receive a reward and end the trial. By varying the location of the probe and the saccade target from trial to trial, an RF map of V4 neurons was generated for different saccade vectors. They found that around the time of the initiation of saccadic eye movements, RFs shrink in size and shift towards the saccadic goal.

Somewhat similarly, neurons in the posterior parietal cortex (Duhamel *et al.*, 1992), frontal eye fields (Umeno and Goldberg, 1997) and superior colliculus (Walker *et al.*, 1995) respond before an impending saccade to stimuli that will be brought into their RFs by that saccade. In other words, the RF of the neuron appears to 'predict' the location where the next eye movement will fall.

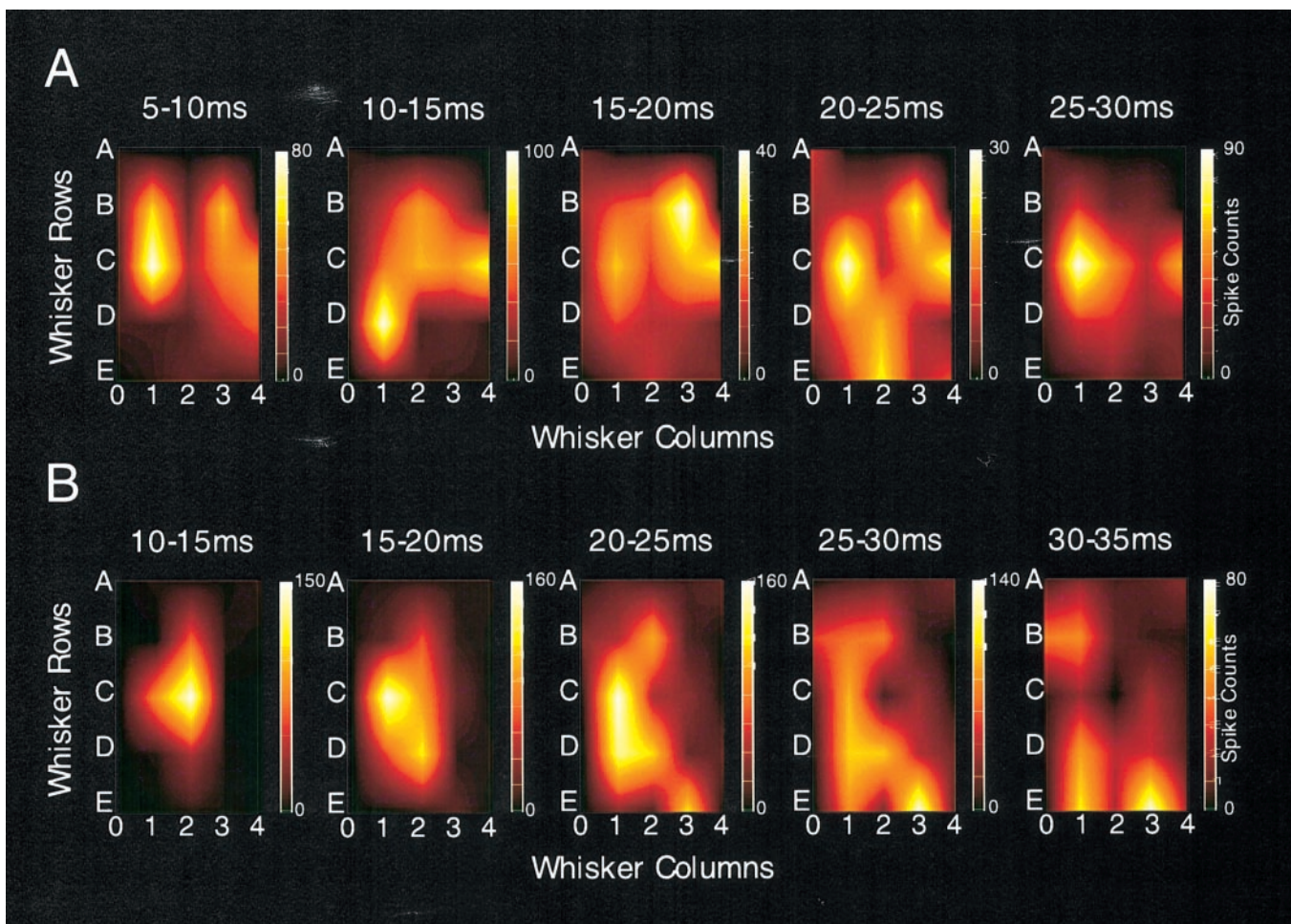### Spatiotemporal Receptive Fields in the Somatosensory Thalamocortical Loop

Traditionally, the RF of a somatosensory neuron is defined as the area of the body surface that, when stimulated, triggers a significant increase in this neuron's firing rate. The rodent somatosensory system has served as the most popular model system for neurobiological studies of this sensory modality. As in other species, classical electrophysiological studies of the 'whisker region' of the rodent somatosensory system have focused on the characterization of the spatial attributes of the RF of neurons located in the subcortical and cortical processing centers of the trigeminal pathway. The 'textbook' description of this pathway suggests that there is a simple one-to-one functional mapping of facial whiskers to the elegant anatomical maps and modules present in the brainstem (barrelets'), thalamus ('barreloids') and cortex ('barrels'). However, more recent quantitative RF mapping studies have shown otherwise by elucidating the widespread and complex evolution of tactile responses along this pathway.

Ventral Posterior Medial Nucleus of the Thalamus of the Rat

To map the RFs of VPM neurons in both space and time, Nicolelis and his colleagues (Nicolelis *et al.*, 1993a; Nicolelis and Chapin, 1994; Faggin *et al.*, 1997) used an approach similar to the response-plane technique. A single neuron's response to the stimulation of ~5 × 5 matrix of whiskers (deflected one at a time) was divided into 5 ms post-stimulus epochs. For each epoch, the whisker that elicited the greatest response (in terms of spike counts) was defined as the 'RF center' for that time epoch. A detailed analysis of the RFs of individual VPM neurons in both awake and anesthetized animals revealed that single VPM neurons have large, multiwhisker RFs whose center is defined by one whisker (the 'principal whisker' or 'PW') whose stimulation elicits the strongest sensory response (Armstrong-James and Fox, 1987; Nicolelis and Chapin, 1994). Importantly, the location of the PW of a given VPM neuron could vary as a function of post-stimulus time (Nicolelis and Chapin, 1994).

VPM neurons could be divided into two functional classes according to the time-dependency of their RF centers. In one class of VPM neurons, the spatial position of the RF center shifted over post-stimulus time. In the other class, neurons exhibited RF centers that remained in the same whisker over time (Nicolelis and Chapin, 1994). The first class of neurons exhibited a spatiotemporal coupling of their RFs since the position of the RF center, and its surround, varied as a function of post-stimulus time. In other words, the PW in the short-latency component (PW_{SL}) was different from the PW in the long-latency component (PW_{LL}) of the response. In general, the spatio-temporal RFs of VPM neurons exhibited time-dependent RF center shifts in a caudal-to-rostral direction. In Figure 3*A*, for example, one particular C→R neuron responded best to its PW_{SL}, whisker C1, at 5–10 ms post-stimulus time while still responding significantly to many other caudal and rostral whiskers which defined its RF surround. By 15–20 ms, the strongest response for this neurons was no longer elicited by whisker C1, but by whisker B3, which became the PW of the RF at long latency (or PW_{LL}). The RF then shifted back to C1. The time-dependent shifting of the centers of these cells' RFs seemed to evolve gradually and appears to involve two factors: (i) an early component composed of short-latency responses from the caudal whiskers; and (ii) a time-dependent enhancement of responses to more rostral whiskers.

Figure 3. (*A*) Spatiotemporal receptive field of a neuron located in the ventral posterior medial nucleus of the rat thalamus. (*B*) Spatiotemporal receptive field of a cortical neuron located in layer V of the rat primary somatosensory cortex. Each color panel represents the matrix of whiskers on the mystacial pad of the animal [whisker columns (or 'arcs') are on the *x*-axis and whisker rows on the *y*-axis] for a given 4 ms epoch of post-stimulus time. The *z*-axis (color) represents the cell's stimulus-evoked spike count for each stimulated whisker. Notice that for each panel the *z*-axis is different. A fourth dimension, post-stimulus time, was represented by plotting a sequence of these 3-D graphs, each representing a 4 ms time epoch.

Conversely, a second class of VPM neurons did not exhibit any evident time-dependent shift in their RFs. Invariably, this group of neurons had their PWs located in the rostral part of the whisker pad which contains small and immobile vibrissae. The RFs of these neurons were characterized by the existence of a single whisker (the PW) which elicited the largest response at all post-stimulus times and by the presence of surrounding whiskers which constituted the RF surround.

The Primary Somatosensory Cortex

With few exceptions (Armstrong-James and Fox, 1987; Armstrong-James *et al.*, 1992), most studies of rat SI cortex focused primarily on the spatial aspects of cortical RF organization. Based on these studies, it was concluded that neurons located within a given barrel cortical column respond preferentially to the deflection of one 'principal' whisker (PW) and fire less vigorously to stimulation of several adjacent whiskers that define the surround region of the neuron receptive field (SRF) (Simons, 1978; Chapin, 1986; Armstrong-James and Fox, 1987). As in the VPM, responses to the PW occur at shorter latencies than responses to whiskers in the SRFs (Armstrong-James and Fox, 1987). Although Armstrong-James *et al.* (Armstrong-James *et al.*, 1992) had proposed and documented the existence of a

time-dependent spread of cortical recruitment [for a review see Moore *et al.* (Moore *et al.*, 1999)], no one had yet characterized the spatiotemporal organization of single SI cortical neuron RFs. Recently, Ghazanfar and Nicolelis (Ghazanfar and Nicolelis, 1999) investigated whether the differences in latency observed between a stimulus applied to a PW versus whiskers in the SRFs could be used to define spatiotemporal RFs in layer V of the rat SI cortex. Overall, they observed that 88% of layer V SI cortical neurons exhibited time-dependent shifts in their RF centers (Figure 3*B*), while 11.2% did not. The patterns of these SI cortical spatiotemporal RFs varied widely and four directions of SI cortical RF shifts could be identified: rostral-to-caudal; caudal-to-rostral; dorsal-to-ventral; and ventral-to-dorsal.

Interestingly, at around the same time as this study, two studies examined the synaptic organization of such spatio- temporal RFs in the rat SI cortex (Moore and Nelson, 1998; Zhu and Connors, 1999). Using *in vivo* whole cell recordings under both pentobarbital- and urethane-anesthetized conditions, these studies described the existence of large, multiple-whisker sub-threshold RFs for neurons in granular, supragranular and infragranular layers. Independent of laminar origin, SI cortical neurons had subthreshold RFs that varied as a function of time (Moore and Nelson, 1998) like the suprathreshold RFs studied

extracellularly by Ghazanfar and Nicolelis (Ghazanfar and Nicolelis, 1999). In the study by Zhu and Connors (Zhu and Connors, 1999), the whisker-evoked synaptic responses were related to the neuronal cell types throughout the depth of SI barrel cortex. Neuronal cell types were classified according to intrinsic firing patterns. They found that, regardless of neuron type and laminar location, SI cortical neurons had, on average, RFs that included more than ten whiskers.

What could the function of spatiotemporal RF structure be for the rat? We suggest that, like the delay-tuned combination-sensitive neurons of the bat auditory system, neurons with spatiotemporal RFs in the rat somatosensory system serve to integrate time-varying multiple whisker inputs. Early quantitative studies of the spatiotemporal integration of tactile inputs by this system demonstrated the time-dependence of multiple whisker interactions (Simons, 1985; Simons and Carvell, 1989). Specifically, barrel cortical neuron responses to principal whisker deflections were inhibited if they were preceded (within a certain time window) by deflections of adjacent, surrounding whiskers. Combination-sensitivity has also been observed in the rat barrel cortex and VPM, where the simultaneous deflection of two or three whiskers results in supralinear responses (Ghazanfar and Nicolelis, 1997; Shimegi et al., 1999). Thus, we hypothesize that time-varying stimuli constructed to match the spatiotemporal RFs of somatosensory neurons should evoke supralinear responses from those neurons.

In primates, DiCarlo and Johnson (DiCarlo and Johnson, 2000) have mapped the spatiotemporal RFs of neurons in the primary somatosensory area (area 3b). In this study, random dot patterns and bars were scanned in up to eight directions across the RF of the neurons. They then characterized the RFs, which were located on the distal fingerpads of the subjects, independently for each direction. The firing pattern of the random dot stimulus at each scanning direction was used to reconstruct the two-dimensional pattern of excitation and inhibition, and these patterns were then compared with the firing patterns obtained using different scanning directions. They found that the somatosensory RFs in the primate neocortex could be best described as having three components: (i) a single, fixed excitatory region of short duration; (ii) one or more fixed inhibitory regions adjacent to the excitatory region and synchronous with the excitation; and (iii) an inhibitory region that overlaps the excitatory region partially or totally and is delayed relative (by ~29 ms) to the first two components.

The functional implications for these primate somatosensory RFs are as follows. The first two components, the fixed excitatory and inhibitory regions, can confer selectivity for particular spatial features or patterns of tactile stimuli. The third component, the delayed inhibitory field, can confer directional sensitivity. In support of these ideas, area 3b neurons are known to be spatially selective for form, such as 'Braille-like' letters (Phillips et al., 1988), and can be orientation-sensitive (Hyvarinen and Poranen, 1978). For directional sensitivity, DiCarlo and Johnson (DiCarlo and Johnson, 2000) found that the placement of the delayed inhibitory component could vary as a function of scanning direction. In the preferred direction, the delayed inhibitory component is displaced maximally from the region of excitation, and this displacement is reduced for stimuli presented in non-preferred directions.

Hypotheses Concerning the Origins of Dynamic RFs in the Thalamocortical Pathway

An important and unresolved question concerns the neural circuitry underlying the genesis of spatiotemporal receptive fields. Both feedforward and feedback mechanisms have been proposed to account for the type of cortical and subcortical time-varying RFs described above. These mechanisms are not mutually exclusive. Feedforward mechanisms could include the convergence of multiple cortical neurons that do not exhibit spatiotemporal RFs onto neurons that do. In the auditory system, Oonishi and Katsuki (Oonishi and Katsuki, 1965) proposed that multi-peaked cortical neurons could be the result of the convergence of two or more single-peaked auditory cortical neurons. For the visual system, spatiotemporal RFs of simple cells could arise from the convergence of feedforward inputs from two different classes of LGN neurons, each with different temporal dynamics [lagged versus non-lagged LGN neurons (Saul and Humphrey, 1992)]. In the somatosensory system, recent evidence suggests that thalamic spatiotemporal RFs could be generated by the convergence of asynchronous inputs from the principal and spinal trigeminal brainstem nuclei and feedback afferents from the cortex (Faggin et al., 1997; Krupa et al., 1999).

Feedback cortical circuitry could also be used to generate time-varying RFs. According to this hypothesis, the initial state of widespread excitation of the cortex caused by the onset of the stimulus would be followed by reverberating activity from feedback circuitry (either locally or from other brain regions). This feedback could increase the selectivity of cortical and thalamic neurons over post-stimulus time. For example, mechanisms based on intracortical feedback have been proposed to explain the dynamic feature tuning and increased selectivity over time in V1 neurons (Dinse et al., 1991; Ringach et al., 1997; Cottaris and De Valois, 1998). Computational models of the visual cortex lend support to this hypothesis. For example, Somers et al. (Somers et al., 1995) used a model of layer IV cat primary visual cortex that demonstrated that local intracortical excitation might be a source to generate sharp orientation selectivity in cortical cells which receive weakly tuned thalamo-cortical excitation. This sharp tuning is provided by recurrent cortical excitation. Similarly, Douglas et al. (Douglas et al., 1995) described how a model population of cat visual cortical neurons could use excitatory feedback to amplify feedforward inputs. This time-dependent process can then be used to generate orientation and directional selectivity (Dinse et al., 1991; Ringach et al., 1997).

Testing the Asynchronous Hypothesis for the Generation of Thalamic Spatiotemporal RFs

While many potential mechanisms for dynamic RFs have been proposed, few have been tested experimentally. The VPM thalamus of the rat provides an accessible model system for testing the roles of both the feedforward and feedback pathways in the genesis of spatiotemporal RFs. Nicolelis and colleagues have hypothesized that spatiotemporal VPM RFs are generated via the asynchronous convergence of parallel feedforward inputs from the ascending brainstem pathways and feedback pathways descending from somatosensory cortical areas (Nicolelis et al., 1993a; Nicolelis and Chapin, 1994). The feedforward pathways arise from the principal and spinal trigeminal brainstem nuclei and are known to have different temporal lags. Moreover, feedback connections from a variety of cortical somatosensory areas also converge on VPM neurons (Welker et al., 1988). In this model, the early, short-latency component of VPM RFs would result from inputs from the fast ascending somatosensory lemniscal pathways that include afferents from the principal and

spinal trigeminal complex of the brainstem which terminate on the same neurons in the VPM. The long-latency component of VPM RFs would be the product of cortical feedback inputs onto VPM neurons.

Two types of experiments tested whether an asynchronous convergence of inputs could account for the generation of spatio-temporal RFs in the rat VPM nucleus. First, the contribution of feedforward somatosensory pathways for the genesis of their RFs was tested by inducing reversible deafferentations of the whisker pad through subcutaneous infusions of a local anesthetic, lidocaine. This local anesthetic allowed measurements of changes in RF organization that emerge as a consequence of altering the flow of tactile information through ascending feedforward trigeminal somatosensory pathways to the VPM and SI cortex (Nicolelis *et al.*, 1993b; Faggin *et al.*, 1997). As predicted, this reversible peripheral deafferentation induced immediate reorganization in both the spatial and temporal properties of VPM and SI RFs. The two major effects were: (i) a temporal shift resulting in the elimination or reduction of early, short-latency component of RFs, located within the 'anesthetized zone', with the enhancement of the later components; and (ii) a spatial shift where RFs that were originally centered in the 'anesthetized region' of the whisker pad shifted, immediately following the induction of the deafferentation, to neighboring territories of the whisker pad. These experiments suggest that peripheral deafferentation largely affects the early, feedforward components of the VPM and SI cortical RFs.

In a second series of experiments, the potential role of cortico-fugal projections in the genesis of spatiotemporal structure of VPM RFs was investigated (Ghazanfar *et al.*, 1997; Krupa *et al.*, 1999). Using a combination of multi-site chronic microwire arrays and a stereotaxically placed cannula, SI cortex was pharmacologically inactivated using the GABA agonist, musci-mol. The RFs of VPM neurons were mapped before and during inactivation. These experiments revealed that corticofugal projections contribute to the genesis of both the short and longer latency neuronal responses in the VPM nucleus. As men- tioned before, these long-latency components are critical to the definition of spatiotemporal RFs in VPM (Nicolelis and Chapin, 1994). These VPM neuronal RF changes via corticothalamic projections likely occur through a combination of direct inputs to the VPM from somatosensory cortex and indirect effects via the cortical influences on the reticular nucleus (Lee *et al.*, 1994) and the trigeminal brainstem (Jacquin *et al.*, 1990).

The results obtained with both peripheral deafferentation and inactivation of corticofugal projections provide general support for the asynchronicity hypothesis and demonstrate that spatio-temporal RFs, at least in the rat VPM thalamus, are defined by large-scale interactions between brain structures.

Further Evidence for Large-scale Interactions in the Definition of RFs
Data from guinea pig and bat auditory systems suggest that experience can modify the RF properties of neurons and that these modifications are 'system' phenomena – not the effects specific to one anatomical structure within the auditory path-way. Using tone-shock pairings, Weinberger and colleagues have shown that such a stimulus–stimulus association results in rapid RF plasticity in the form of increases in tuning to the conditioned stimulus in A1 of guinea pigs (Weinberger and Diamond, 1987). Importantly, such plasticity is thought to arise via the con-vergence of unconditioned and conditioned responses in the medial geniculate of the thalamus followed by activation of the

cholinergic system of the basal forebrain. The release of acetyl-choline engages the stimulus-specific 're-tuning' of the auditory cortex (Bjordahl *et al.*, 1998; Weinberger, 1998). Thus, as suggested by studies in the rat somatosensory system, RF structure and dynamic auditory neurons are likely to be the result of the specific convergence of afferents from multiple structures.

An elegant series of studies by Suga and colleagues has shown how the auditory corticofugal pathway of bats can modify the spectrotemporal RFs of neurons in subcortical structures. The delay-tuned neurons in the bat auditory cortex, medial genicu-late nucleus and inferior colliculus have facilitated responses to emitted pulses and their echoes when the echo returns with a particular delay. Yan and Suga (Yan and Suga, 1996) showed that electrical stimulation of cortical delay-tuned neurons increased the delay-tuned responses of collicular neurons tuned to the same echo delay, and decreased the responses of collicular neurons tuned to different delays. Similar results were seen for the influence of cortical neurons on the frequency tuning of subcortical neurons (Zhang and Suga, 1997; Zhang *et al.*, 1997). A working hypothesis for these results is that there is a re-verberating loop of cortico-thalamo-cortical activity. Specifically, the corticofugal system causes subcortical RF changes which in turn boost cortical RF changes (Gao and Suga, 2000).

Development of Dynamic Receptive Fields
Although there is a paucity of data on the development of spatiotemporal RFs, a few experiments suggest that dynamic RFs require post-natal experience to develop normally. In the visual system, DeAngelis *et al.* (DeAngelis *et al.*, 1993) have shown that the spatial and temporal features of simple cell RFs of the cat visual cortex mature at different times. By mapping RFs during development, they have demonstrated that the spatial properties are adult-like at ~8 weeks postnatally. In contrast, the temporal properties of simple cell RFs do not mature until much later (DeAngelis *et al.*, 1993). Similarly, in the cat LGN, the spatial properties of RFs mature well before the temporal properties, and the time course of LGN RF development seems to slightly precede that of the visual cortex (Cai *et al.*, 1997). These data suggest that perhaps some active experience on the part of the animal may be necessary for the normal development of spatio-temporal visual RFs.

Nicolelis and colleagues have investigated the role of experi-ence on the development of RFs in the rat somatosensory system by eliminating the active movement of their facial whiskers early in development (Nicolelis *et al.*, 1996; Oliveira *et al.*, 1997). Because active tactile exploration plays a critical role in the normal development of haptic perception in mammals (Bushnell and Boudreau, 1991), Nicolelis *et al.* (Nicolelis *et al.*, 1996) postulated that the spatiotemporal RFs of VPM thalamic neurons in the rat probably reflect the pattern of spatiotemporal whisker inputs that occurs during the active 'whisking' of object surfaces. To test this hypothesis, they denervated the facial muscles used during whisker movements by sectioning the facial nerve in early postnatal life. Denervations were performed before these animals experienced any sort of active whisker movements, but after the maturation of the trigeminal system. Facial nerve denervation prevented rats from making active whisker movements on one side of the face throughout their development and adulthood without affecting the sensory innervation of the whiskers, which is provided by the infra-orbital nerve, of their facial vibrissae. After the rats reached adulthood, they examined the spatiotemporal structure of

VPM somatosensory RFs as described above. Preventing the expression of active tactile exploration during development dramatically altered the spatiotemporal RF organization of VPM neurons. First, the size of neuronal RFs was significantly reduced. The reduction was on average from 13 (normal animals) to six whiskers (animals with facial nerve section). Second, the spatiotemporal organization of RFs was disrupted in the VPM. In rats with neonatal facial nerve sections, only 19% of VPM neurons with PW_{SL} in the caudal whisker pad exhibited time-dependent shifts in their RF centers, compared with 100% in normal animals. In other words, preventing these animals from actively exploring their environment during development dramatically reduced the dynamic properties of VPM neurons.

These results from the cat visual and rat somatosensory systems underscore the importance of active movements for the functional maturation of normal spatiotemporal RFs in both cortical and subcortical relays and implicate experience-dependent mechanisms for the establishment of spatiotemporal RFs.

Defining Receptive Field Dynamics

The findings reviewed above demonstrate the fundamental relevance of time in the RFs of auditory, visual and somatosensory thalamocortical neurons. In conjunction with these findings, experiments which demonstrate plasticity of neuronal properties during learning and experience (Recanzone *et al.*, 1993; Wang *et al.*, 1995a) and injury (Florence and Kaas, 1995), suggest that, fundamentally, mammalian sensory systems can no longer be considered as hierarchical collections of passive filters or feature extractors that are specialized in detecting the presence of static stimulus attributes. First, the RF structure of thalamocortical neurons is structured to integrate time-varying sensory input. Second, the form of time-varying sensory input that is most efficiently integrated is dependent upon experience, and this experience can be the result of ontogenetic changes, learning and/or injury. Finally, the time-varying RF structure of neurons is generated via the convergence of multiple feed-forward and feedback pathways.

Put in another way, the functional organization of sensory systems reflects their active attempts to compare the meaning encoded in time-varying sensory signals with the accumulated representation of the sensory experiences acquired during evolution and during an individual's lifetime.

Notes

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