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Effects of stimulus duration on neuronal response properties in the somatosensory cortex of the star-nosed mole

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Abstract

Star-nosed moles have a series of mechanosensory appendages surrounding each nostril. Each appendage is covered with sensory organs (Eimer's organs) containing both rapidly adapting and slowly adapting mechanoreceptors and each appendage is represented in primary somatosensory cortex (S1) by a single cortical module. When the skin surface of an appendage is depressed, neurons in the corresponding module in S1 respond in either a transient or sustained fashion. The aim of this study was to characterize and compare the responses of these two classes of neurons to both short (5 or 20 ms) and long (500 ms) mechanosensory stimulation. Activity from neurons in the representation of appendage 11, the somatosensory fovea, was recorded while delivering mechanosensory stimuli to the corresponding skin surface. Transient and sustained neurons had different levels of spontaneous activity and different responses to both short and long mechanosensory stimulation. Neurons with sustained responses had a significantly higher spontaneous firing rate than neurons with transient responses. Transient neurons responded to a 5 ms stimulus with excitation followed by suppression of discharge whereas sustained neurons did not exhibit post-excitatory suppression. Rather, responses of sustained neurons to 5 ms stimuli lasted several hundred milliseconds. Consequently sustained responses contained significantly more spikes than transient responses. These experiments suggest contact to the appendages causes two distinct firing patterns in cortex regardless of the duration of the stimulus. The sustained and transient responses could reflect either the activity of fundamentally different classes of neurons or activity in distinct subcortical and cortical networks.

Key words: *tactile*, *touch*, *mechanosensory*, *S1*, *rapidly adapting*, *slowly adapting*

The star-nosed mole uses its nasal appendages to explore its surroundings through touch. For this purpose the appendages are covered with small (60 μm) mechanosensory Eimer's organs that contain slowly adapting Merkel cell–neurite complexes, rapidly adapting lamellated receptors, and a series of free nerve endings that form swellings just below the outer keratinized epidermis (Catania, 1996). Responses from each Eimer's organ are conveyed through primary afferents to trigeminal brainstem nuclei, to the thalamus, and finally to the somatosensory cortex. The information from the star is represented in three separate cortical maps of the contralateral nose, each visible in sections of the cortex processed for cytochrome oxidase (Catania and Kaas, 1995). In a reflection of its behavioral importance, the representation of the mechanosensory star takes up nearly 40% of the somatosensory cortex. Previous investigations have demonstrated that a stimulus delivered to a point on the star elicits either a transient or a sustained discharge from neurons in primary somatosensory cortex—S1 (Sachdev and Catania, 2002). Similar response patterns have been described in the somatosensory systems of a number of other species (Mountcastle, 1957; Simons, 1978; Sur *et al.*, 1981, 1984; Swadlow, 1989; DiCarlo *et al.*, 1998) and in other sensory systems (see Rowe and Stone, 1977, 1980 for the visual system).

In this study, we examined the relationship between stimulus duration and activity of sustained or transient neurons in S1. It is clear that such neurons respond differently to sustained depression of the skin surface, and this is the basis for their classification. However, it is less obvious how these neurons might differ in response to very short duration stimulation that could, in principle, result in similar patterns of cortical activity across the two neuronal classes. Star-nosed moles typically touch the appendages to the substrate for very brief periods (< 30 ms) during their foraging bouts, but may also contact the nose to objects or the substrate for much longer periods when not actively searching for prey items. Thus the mechanoreceptors are stimulated for different durations at different times. We wondered how the different classes of neurons, sustained or transient, would respond to either long or short duration mechanosensory stimuli. In this study we used very short-lasting stimuli (5 or 20 ms) and a longer lasting stimulus (500 ms) to examine the responses of neurons in the S1 representation of the 11th appendage. The 11th appendage was chosen for

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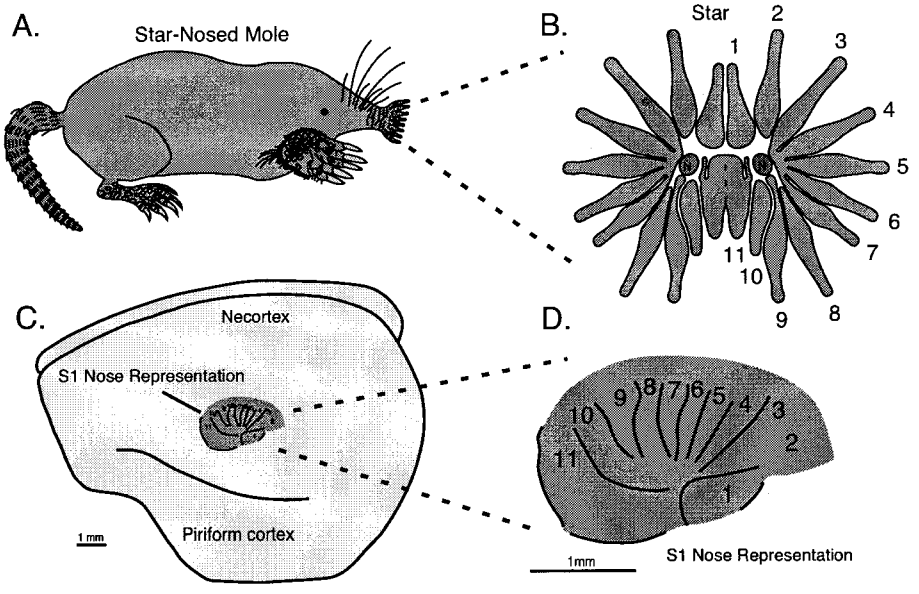

FIGURE 1. Schematic illustration of the star-nosed mole's specialized mechanosensory system and the relationship between the star and its representation in primary somatosensory cortex. (A) The external anatomy of the star-nosed mole (*Condylura cristata*). The 11 appendages on each side of the nose are covered with thousands of sensitive Eimer's organs (not shown). The star is used to explore the environment through touch and does not contain muscles that could be used to manipulate objects. (B) Enlargement of the star showing the 11 appendages that surround each nostril. The lowermost, 11th appendage acts as the somatosensory fovea and has the largest representation in the cortex. (C) The neocortex and relative position of the primary somatosensory area (S1) in lateral cortex. Additional representations of the star are located further lateral in cortex (not shown, but see Catania and Kaas, 1995). (D) Enlargement of the S1 star representation showing arrangement of cortical modules that represent each appendage. Note the greatly magnified representation of the 11th appendage despite its relatively small size on the star (for details see Catania and Kaas, 1995, 1997).

this investigation because it is the tactile fovea of the star and its large representation makes it particularly accessible for cortical recordings (Fig. 1).

Materials and methods

The details of the methods have been described earlier (Sachdev and Catania, 2002). Briefly, four star-nosed moles were used in this study. Animals were anesthetized with a combination of ketamine and urethane (Cowan and Wilson, 1994; Contreras *et al.*, 1996). An initial dose of urethane (1.0 g/kg, i.p.; 15% w/v) was followed by three to four supplemental doses of ketamine (0.1 g/kg of body weight). This combination of anesthetic, administered at the beginning of the experiments, usually induced a surgical plane of anesthesia that lasted for the duration of the recordings. The mole was placed in a head holder, a craniotomy was made and the brain was protected with silicone. A photograph of the cortical surface was used to mark electrode penetrations relative to blood vessels and body temperature was maintained at 37°C. Single tungsten microelectrodes or arrays of four electrodes (four electrodes advanced together with a 200 μm inter-electrode separation, FHC, 1–2 MΩ, at 1,000 Hz) were advanced perpendicular to the surface into layer 4 of somatosensory cortex at a depth of approximately 500 μm. Eighty-seven units were recorded in the course of 9 penetrations (4 electrodes per penetration) of the multi electrode array, whereas 43 units were recorded in 13 penetrations of single electrodes. Receptive fields at each penetration site were mapped on to an enlarged schematic of the nose. Spontaneous activity and stimulus evoked activity was collected with a Multi-Neuronal Acquisition Processor (Plexon Inc., Dallas, TX, sampling rate of 40 kHz per channel). All spike sorting was done twice, once online, and a second time offline using a principal component spike sorting algorithm (Plexon Inc.; Sachdev and Catania, 2002). Additional single units could sometimes be discriminated offline for each electrode. Electrolytic lesions were used to mark selected penetrations. Lesions and photographs of the brain surface were used to reconstruct recording sites relative to the distinctive cytoarchitecture of star-nosed mole layer 4 cortex (Catania and Kaas, 1995). At the end of the recording session, moles were perfused transcardially with (0.9%) saline, followed by 2% paraformaldehyde. The brain was removed and cortex was separated from white matter and flattened between glass plates. Tangential sections were cut parallel to the surface on a freezing microtome and processed for cytochrome oxidase (Wong-Riley and Carroll, 1984). Electrolytic lesions were used in combination with a photograph detailing the locations of electrode penetrations to determine the location of each electrode penetration relative to the star pattern in S1 cortex.

The 11th appendage of the star was stimulated with a blunt probe attached to a piezoelectric wafer controlled by Spike 2 software and a 1401 computer interface (Cambridge Electronic Devices, London). The probe could be adjusted to have a contact area from 0.2 to 0.5 mm across. The stimulus had a rapid onset and offset (0.2 ms) and indented the skin approximately 200 μm. Stimuli (5, 20, 500 or 1,000 ms) were presented at 1 s intervals. The 5 and 500 ms stimuli were used for all neurons in the sample and this condition forms the basis for much of the comparison between sustained and transient neurons. We compared the effectiveness of the 5 and the 20 ms stimuli (Fig. 2) and found an equal or better response from the 5 ms stimulus as measured by number of spikes evoked in the 100 ms following the stimulus onset. The 5 ms stimulus was chosen for the bulk of our analysis because this stimulus was shorter than the duration of response for any cortical neuron.

Neuroexplorer software (Plexon Inc.) was used for online and offline analysis of single unit data. For all units both 1 and 10 ms binned histograms were prepared offline. Neurons that responded with a persistent discharge greater than the mean spontaneous rate (200 ms before stimulus onset) for the entire 500 ms stimulus were classified as having a sustained discharge. In addition, confidence intervals of the 10 ms PSTH were examined to determine whether the increase in firing rate was significant throughout the stimulus. In a portion of these neurons the tail end of the sustained response barely reached significance (Fig. 4). For the transient neurons, the response always reached significance for at least two 10 ms bins. Population histograms were generated by averaging PSTHs generated during each stimulus condition. Non-parametric tests (Mann–Whitney U and Wilcoxon) were used to assess significance. All procedures used in this study conformed to National Institutes of Health standards concerning the use and welfare of experimental animals and were approved by the Vanderbilt University Animal Care Committee.

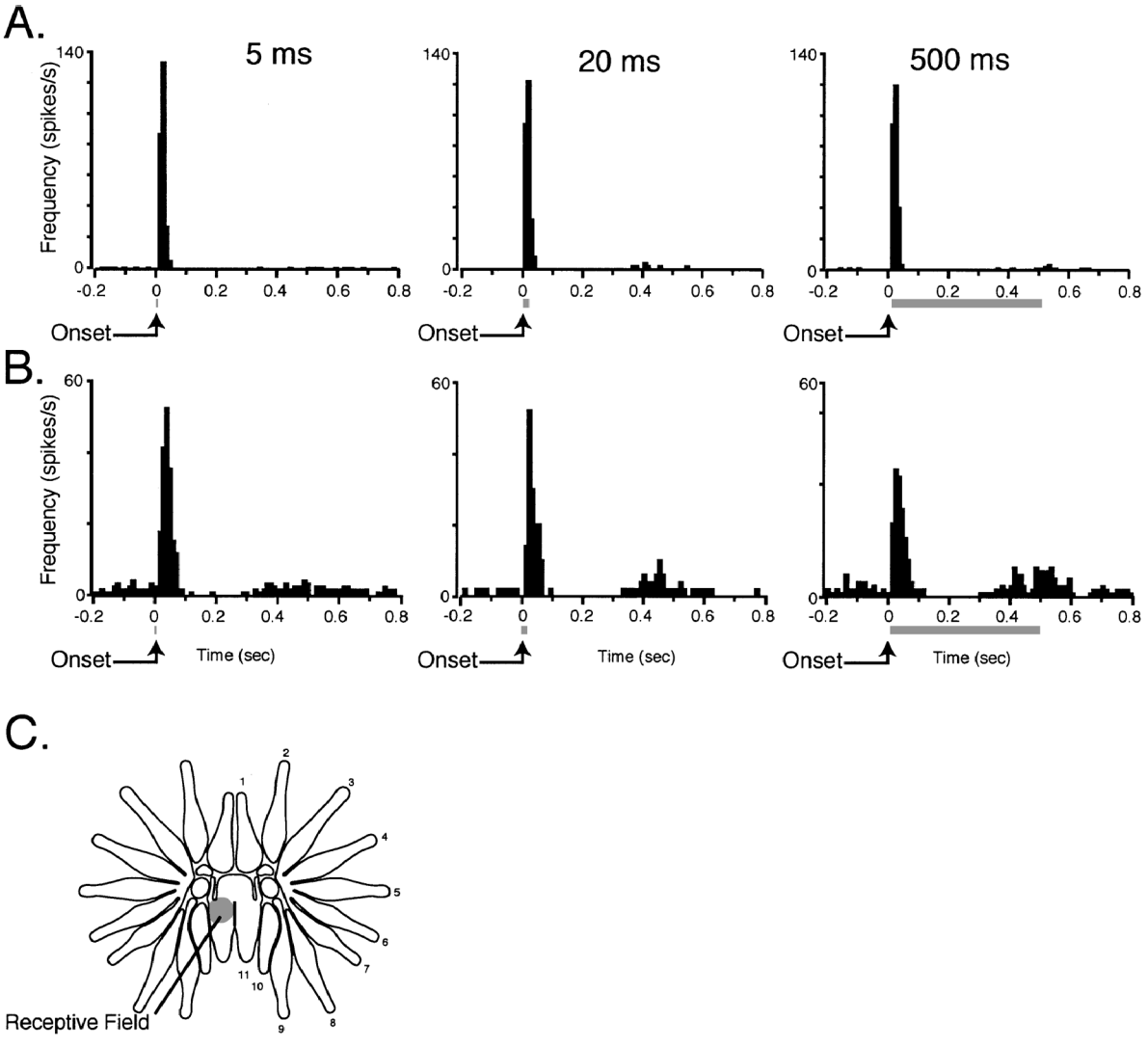

FIGURE 2. Effect of stimulus duration on transient responses. For these neurons (separate neurons in A and B), increasing the stimulus duration from 5 to 500 ms had no effect on the transient response at stimulus onset. The response to the 5 ms stimulus was indistinguishable from the response to the 20 ms stimulus. The 500 ms stimulus illustrates the transient nature of these cells' response to sustained skin depression. Note the post-excitatory suppression in spontaneous activity in (B). In panel (A), the spontaneous activity (activity before stimulus onset) was less than 0.5 Hz. The gray bars indicate stimulus duration. Bin size is 10 ms.

Results

Activity was recorded from 130 neurons in the cortical representation of the 11th appendage. All neurons were tested with the 5 and 500 ms stimuli; ten were tested with a 20 ms stimulus, and five were tested with a 1,000 ms stimulus. The spontaneous rate of discharge for all neurons was 1.72 Hz (SE = 0.14). To initially classify the neurons as either transient or sustained in their response properties, each was tested with the 500 ms stimulus at the center of their receptive field on the 11th appendage. Ninety-six neurons responded to this stimulation with a transient discharge at the stimulus onset (Fig. 2) and 34 neurons responded with a sustained discharge—lasting for the duration of the stimulus (Figs. 3, 4). Eighty-seven neurons (63 transient neurons and 24 sustained neurons) responded to stimulus offset (Fig. 4), typically (in 83 of 87 neurons) with an excitatory discharge.

Responses of sustained and transient neurons

There were two main classes of neurons that differed in their responses to sustained depression of the skin surface. The bottom panel of Figure 5 shows average post-stimulus time histograms for these different classes of neurons responding to a 500 ms stimulus. Transient neurons generally responded with brief excitation followed by post-excitatory suppression of activity, whereas sustained neurons responded with a sustained elevation of their activity throughout the duration of the stimulus. Most of the neurons in both classes responded to stimulus offset with excitation. Both classes of neurons were often encountered in a single electrode penetration.

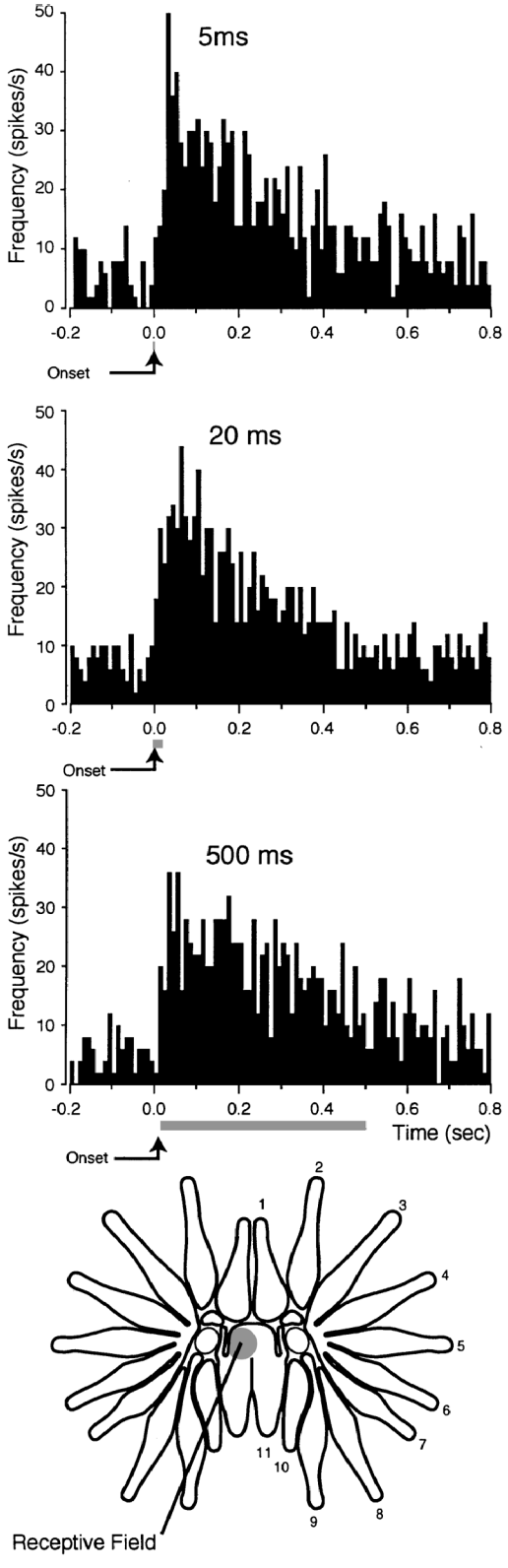

FIGURE 3. Response from a single neuron with a sustained response to skin depression. Stimulation lasted for 5 ms (top), 20 ms (middle) and 500 ms (bottom). The 5 and 20 ms stimuli evoke similar responses that are distinguished from the longer response to the 500 ms stimulus.

The same neurons were then tested with the 5 ms stimulus to determine how the time-course and magnitude of their responses differed for a stimulus that was presumably too brief to modulate much of the ongoing neuronal activity. The short, 5 ms stimulus evoked qualitatively different responses in the two classes of neurons. In neurons with a sustained response to the 500 ms stimulus (sustained neurons) a 5 ms stimulus produced no evidence of post-excitatory suppression (Figs. 3–5). Instead, the responses of the sustained neurons generally trailed off slowly and approached the spontaneous discharge rate over several hundred milliseconds. In contrast, for transient neurons a 5 ms stimulus was followed by suppression of firing for 42% of the cells (Figs. 2b, 5). Maximal post-excitatory suppression occurred at a latency of approximately 150 ms. Twenty transient neurons had a low spontaneous firing rate making it impossible to determine whether there was in fact post-excitation suppression of activity (for example, Fig. 2a). As a consequence of their prominent post-excitatory suppression, transient neurons had significantly fewer spikes than sustained neurons in the first 100 ms after the 5 ms stimulus (MWU, $p < 0.001$). For example, the average number of spikes evoked by the 5 ms stimulus in the first 100 ms post-stimulus was 50.4 (SE = 3.4 spikes) in the transient neurons and 73 (SE = 7.1 spikes) in the sustained neurons (Fig. 5). In the 200 ms post-stimulus there were an average of 58.1 spikes evoked in the transient (SE = 3.8 spikes) and 125 spikes (SE = 14.3 spikes) evoked in the sustained neurons.

Most transient and sustained neurons also responded to the offset of the 500 ms stimulus with significantly different numbers of spikes (Mann–Whitney U, $p < 0.001$). The number of spikes in the 100 ms post-stimulus offset was 30.8 spikes (SE = 3.2 spikes) and 48.2 spikes (SE = 5.1 spikes) for the transient and sustained neurons, respectively. In the 200 ms post-stimulus, the stimulus evoked 42.3 spikes (SE = 4.5 spikes) in the transient and 85.9 spikes (SE = 9.1 spikes) in the sustained neurons.

Finally, the rate of spontaneous activity for the sustained neurons was significantly higher than for transient neurons (MWU, $p < 0.001$). The spontaneous rate of firing was 2.33 Hz (SE = 0.33 Hz) for sustained and 1.57 Hz (SE = 0.15 Hz) for all transient neurons. Transient neurons recorded in the same penetration ($n = 18$) as the sustained neurons had a mean rate of 1.47 (SE = 0.32 Hz). Removing all transient neurons that had low (< 0.2 Hz) or no spontaneous activity (as was done to prepare the average transient histograms in Fig. 5) did not alter this measure of the firing rate.

Discussion

Star-nosed moles explore their environment and search for prey by making a series of short rapid touches with the star, but the star may also be held in place for brief periods or make more prolonged contact to prey items during feeding. One goal of this study was to determine how cortical neurons in the S1 star representation respond to different durations

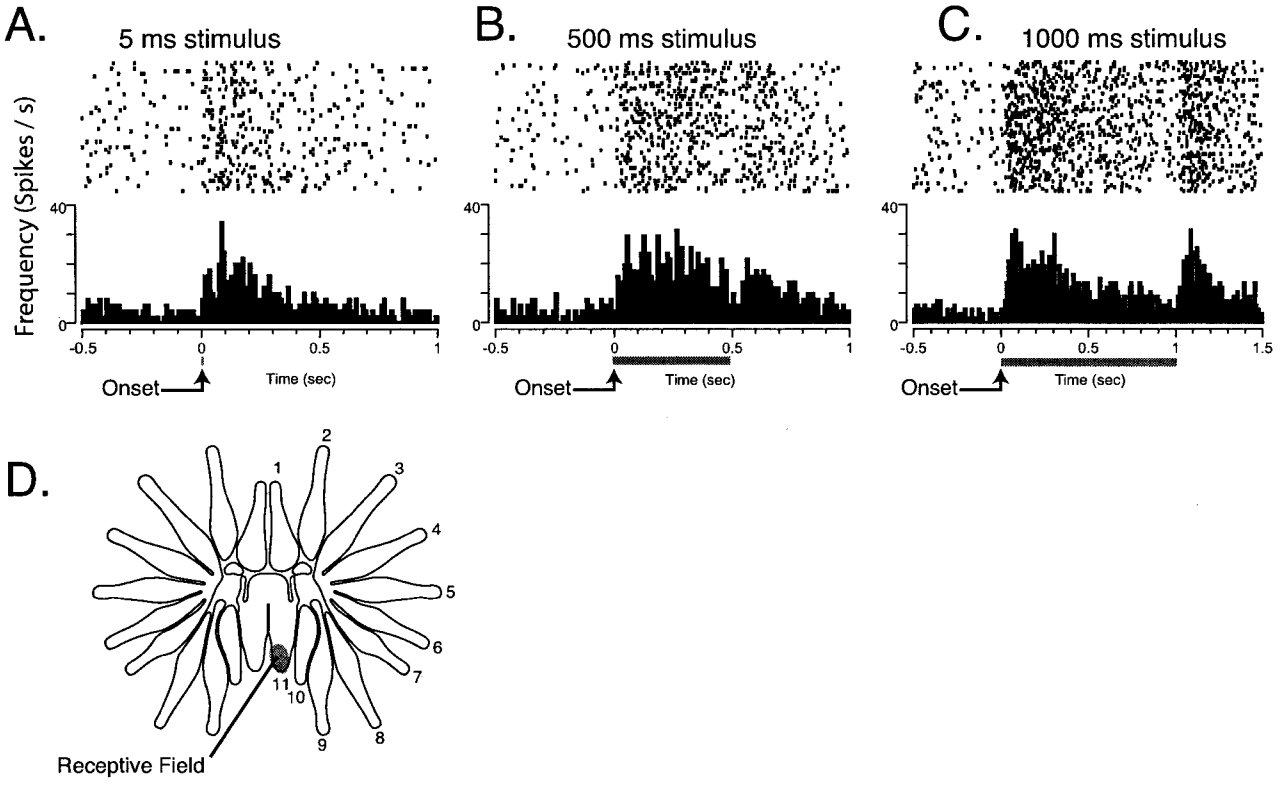

FIGURE 4. Effect of stimulus duration on a neuron with a sustained response to stimulation. The 5 ms stimulus (A) evoked a response that lasted for approximately 300 ms (compare with Fig. 2). The 500 ms stimulus evoked a response that lasted throughout the stimulus, although the response begins to trail off before stimulus offset at 500 ms. Similarly the 1 s stimulus evoked a response that lasted throughout the stimulus but decreased over time (for the 1,000 ms trials there was a 1 s interval between each 1,000 ms of stimulation). Note the response to stimulus offset at the end of the 500 and 1,000 ms stimuli. Bin size is 10 ms.

of contact to the skin surface of the star. Our main finding was that at least two temporally overlapping but distinct patterns of cortical activity occur in response to both short and long duration contacts to the skin surface. One class of cells responded with a transient excitatory discharge that lasted for less than 100 ms post-stimulus and was followed by suppression of neuronal activity. A second class of cells responded with a sustained excitatory discharge that continued for several hundred milliseconds beyond the offset of the stimulus. These differences in response profiles were evident even with a short, 5 ms stimulus. Therefore, it is not simply the case that sustained neurons are following the stimulus duration, at least for short contacts. For example, a 5 ms stimulus and a 20 ms stimulus (both within the range of contacts that occur during star-nosed mole foraging behavior) result in similar responses of sustained neurons that last several hundred milliseconds—far longer than the duration of contact.

Sustained and transient neurons have been described in a number of previous studies. For example, a rapidly adapting and slowly adapting pattern have been described in the peripheral somatosensory system of primates (Mountcastle *et al.*, 1972; LaMotte and Whitehouse, 1986; Johnson and Hsiao, 1992; Vega-Bermudez and Johnson, 1999). The slowly adapting peripheral discharge has been linked to pattern (form and texture) discrimination whereas the rapidly adapting discharge has been linked to the detection of flutter (Mountcastle *et al.*, 1972). Though both transient and sustained patterns of discharge occur in the somatosensory cortex of primates (Mountcastle and Powell, 1959; Paul *et al.*, 1972; Sur *et al.*, 1984), rats (Simons, 1978) and rabbits (Swadlow, 1989) the precise relationship between the peripheral discharge pattern and cortical discharge patterns is not clear (see DiCarlo *et al.*, 1998 for a discussion). It has been suggested (DiCarlo *et al.*, 1998) that the sustained firing pattern is generated by central, rather than peripheral mechanisms. Functionally, the transient neurons may be concerned primarily with new tactile input (or with movement across a skin surface) whereas the sustained neurons could be concerned with pattern discrimination (however, see Rowe and Stone, 1980; DiCarlo *et al.*, 1998). This is particularly interesting in the case of star-nosed moles, because the Eimer's organs contain a series of free nerve endings that have been theorized, based on structure and distribution, to code for pattern discrimination (Catania, 2000). Determining the response properties of primary afferents from the different components of Eimer's organs would be a useful next step to understanding how the different classes of cortical cells may code for different stimulus parameters.

At least two mechanisms for generating transient and sustained responses can be suggested. For

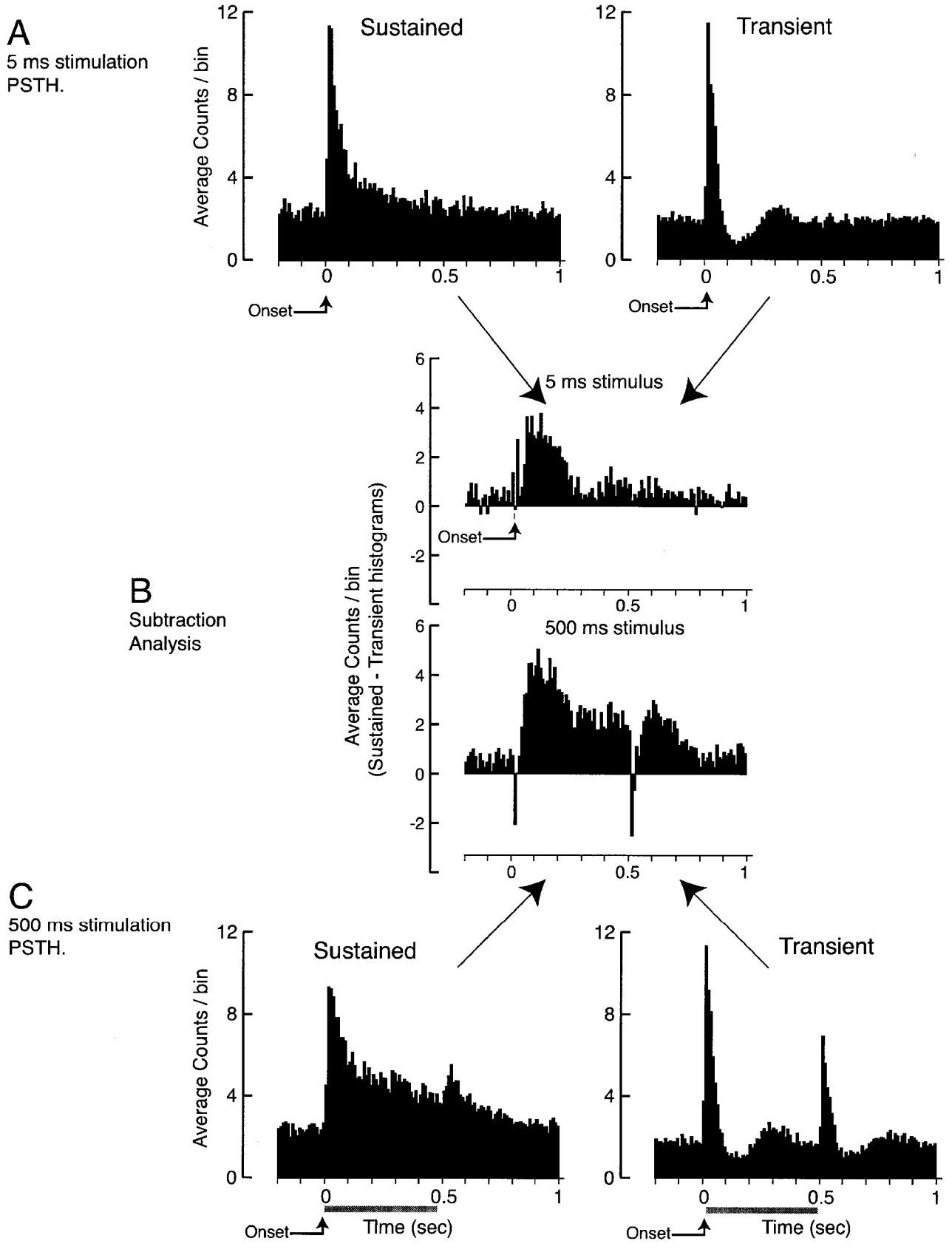

FIGURE 5. Average post-stimulus time histograms of transient and sustained neurons for 5 and 500 ms stimuli, with a subtraction histogram of sustained and transient neurons. The neurons that respond in a sustained fashion show no suppression of activity after the excitatory response and thus have a higher post-stimulus discharge rate for both stimulus conditions. For the 500 ms stimulus the initial average response of the transient neurons is greater than the response of the sustained neurons. It is also interesting to note the negative bins in the subtraction histogram for the 500 ms, but not 5 ms condition. This difference may be the result a combined "on response" and "off response" for the 5 ms stimulation of the sustained neurons (left top panel), whereas these two responses are separated in time for the 500 ms condition (bottom left). Bin size is 10 ms. A total of 76 neurons with a non-zero (> 0.5 Hz) spontaneous activity were used to prepare the average transient histograms.

example, the transient and sustained patterns could result from intrinsic membrane properties. If so, transient and sustained neurons could be two different classes of cortical neurons with distinct voltage gated currents, such as different class of cortical neurons (pyramidal as opposed to fast spiking interneurons) or simply different subclasses of pyramidal neurons (McCormick *et al.*, 1985; Chagnac-Amitai *et al.*, 1990; Kawaguchi, 1993; Kawaguchi and Kubota, 1993). Alternatively these different classes of response could occur as a result of different inputs to otherwise similar neurons. There may of course also be a combination of these factors that contribute to the output of the different classes of neurons. These alternatives may be further explored by investigation of subcortical inputs to S1.

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