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Convergence of Submodality-Specific Input Onto Neurons in Primary Somatosensory Cortex

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¹Krieger Mind/Brain Institute and ²Department of Neuroscience, Johns Hopkins University, Baltimore, Maryland; ³Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan County, Taiwan; and ⁴Department of Psychological and Brain Sciences, Indiana University, Indiana

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Pei Y-C, Denchev PV, Hsiao SS, Craig JC, Bensmaia SJ. Convergence of submodality specific input onto neurons in primary somatosensory cortex. *J Neurophysiol* 102: 1843–1853, 2009. First published June 17, 2009; doi:10.1152/jn.00235.2009. At the somatosensory periphery, slowly adapting type 1 (SA1) and rapidly adapting (RA) afferents respond very differently to step indentations: SA1 afferents respond throughout the entire stimulus interval (SUSTAINED response), whereas RA afferents respond only at stimulus onset (ON response) and offset (OFF response). We recorded the responses of cortical neurons to step indentations and found many neurons in areas 3b and 1 to exhibit properties that are intermediate between these two extremes: These neurons responded during the sustained portion of the stimulus and also at the offset of the stimulus. Several lines of evidence indicate that these neurons, which exist in large proportions even at these early stages of somatosensory cortical processing, receive input from both populations of afferents. First, we show that many cortical neurons have both a significant SUSTAINED response and a significant OFF response. Second, the strength of the OFF response is uncorrelated with that of the SUSTAINED response, which is to be expected if SUSTAINED and OFF responses stem from different populations of afferent fibers. Third, the bulk of the variance in cortical responses to step indentations can be accounted for using a linear combination of both SA1 and RA responses. Finally, we show that the OFF response in cortical neurons does not reflect rebound from inhibition. We conclude that the convergence of modality specific input onto individual neurons is common in primary somatosensory cortex and discuss how this conclusion might be reconciled with previous findings.

INTRODUCTION

SA1 and RA afferents can readily be distinguished on the basis of the temporal profiles of their responses to step indentations: SA1 afferents produce a sustained response, whereas RA afferents produce transient responses at the onset and offset of the stimulus. Neurons in primary somatosensory cortex (SI) have also been categorized based on the temporal profiles of their responses to indentations: Some neurons respond throughout the stimulus interval, whereas others respond only at the onset and offset of the indentation. The adaptation properties of cortical neurons have been interpreted to indicate the source of their peripheral input: Neurons that exhibit sustained responses are thought to receive input from SA1 afferents; neurons that exhibit transient responses and no sustained response belong to the RA pathway.

Because there are two intervening synapses between periphery and cortex—one in the dorsal columns nuclear complex

(DCNC) and the other in the ventroposterior nucleus of the thalamus (VPN)—the interpretation of the adaptation properties of cortical neurons is not unequivocal. The use of adaptation properties to infer submodality input, however, receives support from what is known of the earlier processing stages. Indeed, individual neurons in the DCNC exhibit responses similar to those of a single type of peripheral afferent in macaque (Douglas et al. 1978), and their responses seem to be dominated by input from one or a few mechanoreceptive fibers (Ferrington et al. 1987a,b). Similarly, neurons in VPN are readily classifiable as SA1-, RA- or PC-like (Kaas et al. 1984). In other words, signals stemming from SA1 and RA afferents seem to be segregated as they ascend the perceptual pathway. The segregation of modality-specific signals along the somatosensory pathway is also reflected in a functional segregation of processing streams: the SA1 stream is thought to mediate form and texture perception, whereas the RA stream is thought to underlie flutter perception and motion detection (Johnson 2001).

The degree of segregation of SA1 and RA signals in SI of primates has not been investigated systematically and quantitatively. Sur et al. (1981, 1984) distinguished neurons in macaque SI based on the presence or absence of an observable sustained response. However, many neurons that exhibited a sustained response also produced an OFF response, a characteristic of RA but not SA1 afferents at the somatosensory periphery.¹ Dykes and colleagues (Dykes and Gabor 1981; Dykes et al. 1980) made a similar observation in cat SI. In other words, neurons classified as SA1-like also exhibited RA-like response properties. In this study, we assess the degree to which individual neurons in SI exhibit responses to step indentations that are analogous to those produced by one or both types of peripheral afferents. The objective of this line of inquiry is to assess the extent to which submodalities remain segregated in SI. Specifically, we assess whether submodalities remain segregated in SI or whether individual neurons receive convergent input from both SA1 and RA afferents.

METHODS

Neurophysiology

The procedures have been described in detail in previous papers (Bensmaia et al. 2008; Muniak et al. 2007) and therefore are only summarized here. All experimental protocols complied with the guidelines of the Johns Hopkins University Animal Care and Use

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¹ Pacinian (PC) afferents, another class of rapidly adapting afferents, also exhibit OFF responses and an absence of a SUSTAINED response.

Committee and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Peripheral experiments

Single-unit recordings were made from the ulnar and median nerves of four anesthetized macaque monkeys (*Macaca mulatta*) using standard methods (Talbot et al. 1968). Standard procedures were used to classify mechanoreceptive afferents (Freeman and Johnson 1982; Muniak et al. 2007; Talbot et al. 1968).

Cortical experiments

Extracellular recordings were made in the postcentral gyri of one hemisphere of each of five awake macaque monkeys using previously described techniques (Mountcastle et al. 1991). The monkeys received fluid rewards at random intervals (ranging from 2 to 10 s), which was sufficient to keep them alert through the recording period. On each recording day, a Reitbock multielectrode microdrive (Mountcastle et al. 1991) was loaded with seven quartz-coated platinum/tungsten (90/10) electrodes (diameter, 80 μm ; tip diameter, 4 μm ; impedance, 1–3 Ω at 1,000 Hz). The electrodes were driven into the cortex until they encountered neurons in area 1 with receptive fields (RFs) on the distal fingerpad. A day spent recording from area 1 was typically followed by a day spent recording from area 3b. We distinguished area 3b from area 1 based on the systematic progression of RF locations as the electrodes are advanced into the cortex. Cutaneous RFs of neurons near the cortical surface usually occupied a portion of a single digit. As the electrode was advanced deeper into the cortical tissue, the location of the RF shifted toward the base of the finger and often extended into the palmar whorls (at $\sim 1,500$ – $2,000$ μm below the 1st sign of neural activity). As the electrode was advanced further, the RF location began to move back onto the glabrous surface of the proximal phalanx and was much more localized. This reversal has been verified histologically in previous studies to correspond to the

border between areas 3b and 1 (DiCarlo et al. 1998). Over the next 500–1,000 μm , the RF locations continued to move distally along the glabrous surface of the digit without discontinuities. Neurons with RFs located on one of the distal fingerpads in area 3b were typically located in a region 2,000–3,000 μm below the first signs of neural activity. We recorded from neurons whose RFs were located on the distal pads of digits 2–5. After recording from area 1 and 3b at a given location, the electrode array was shifted ~ 200 μm along the postcentral gyrus until the entire representation of digits 2–5 had been covered.

Recordings were obtained from neurons in areas 3b and 1 that met the following criteria: 1) action potentials were well isolated from the background noise (Fig. 1, *top left inset*); 2) the RF of the neuron included at least one of the distal finger pads on digits 2–5; and 3) the stimulator array could be positioned so that the RF of the neuron was centered on the array. None of the neurons that we studied had Pacinian-like (PC-like) properties (i.e., exhibited rapidly adapting responses, had large RFs, and responded to light puffs of air).

Stimuli

The stimuli were generated and delivered using a tactile stimulator consisting of 400 independently controlled probes arrayed over a 1-cm² area (Killebrew et al. 2007). The center to center distance between probes is 500 μm . Each probe has a diameter of 300 μm and a maximum displacement (depth of indentation) of 2 mm. The stimulator allowed us to reliably deliver ramp-and-hold indentations with an accuracy of ~ 5 μm . Ringing at stimulus onset and offset was minimized by implementing notch filters, each tailored to reduce the resonance of individual probes. The probes were indented into the skin ~ 1 mm beyond initial contact to increase the stimulated area. Such preindentations have been shown to have little effect on afferent responses after these have been allowed to adapt (Vega-Bermudez and Johnson 1999).

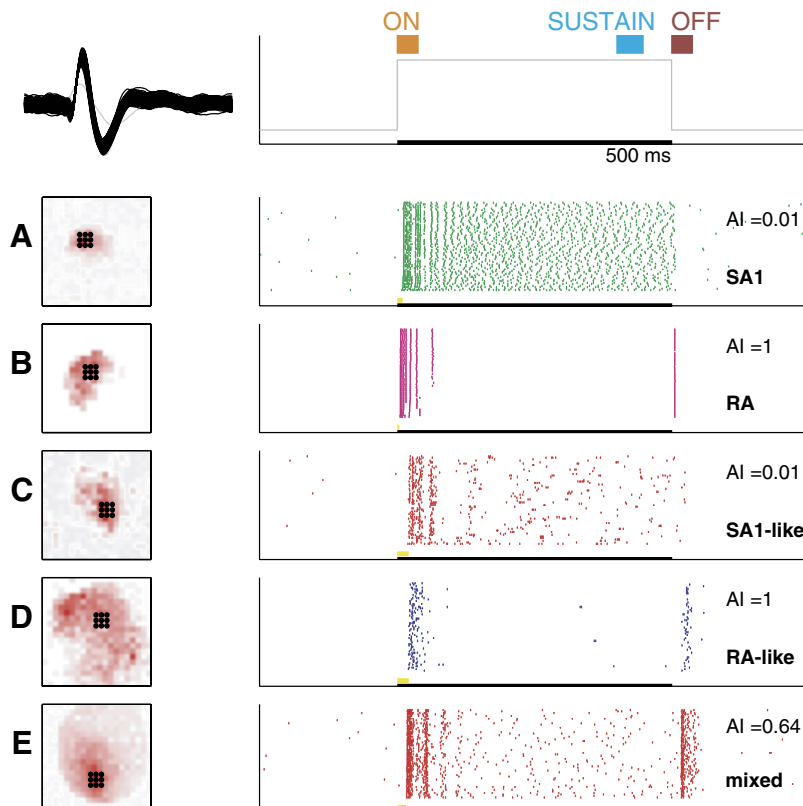


FIG. 1. *Top left inset*: 892 accepted spikes (black) and 1 rejected spike (gray) of a representative isolation in area 1 (3-ms trace). Responses of a typical slowly adapting type 1 (SA1) (A) and rapidly adapting (RA) (B) afferent to 60 repeated presentations of a step indentation (*top right inset*); the gray trace in the *inset* shows the ideal stimulus trajectory. C: responses of an SA1-like neuron in area 3b. D: response of an RA-like neuron in area 1. E: response of a neuron that exhibits both SA1-like and RA-like responses in area 3b. The adaptation index, AI, is a function of the ratio of the OFF response to the SUSTAINED response, each normalized by their population means. As reflected in the ON responses, there was a slight ringing in the stimulus after its onset. Notch-filters were used to dampen it, but these did not eliminate it completely. In all analyses, we ensured that the SUSTAINED response was measured after the ringing had subsided. The yellow bar shows the response latency. The RF of each neuron, measured using from data obtained in the RF-mapping protocol, is shown to the *left* of the corresponding raster plot, along with the locations of the 9 probes (centered on the hot spot) indented in the adaptation and variable-durations indentations protocols.

RECEPTIVE FIELD MAPPING. This protocol was used to identify the neuron's point of maximum sensitivity (or hot spot) and the spatial extent of its RF. On each trial, one of the 400 probes, selected pseudo-randomly, was indented 300 μm into the skin for 100 ms (including the ramps). The duration of the ON- and OFF-ramps was 25 ms (as was the case for all the protocols) and the interstimulus interval was 100 ms. Each probe was indented five times for a total of 2,000 trials. The neuron's hotspot was defined as the location on the skin that produced the highest firing rate when stimulated.

ADAPTATION PROTOCOL. This protocol was used to gauge the extent to which individual neurons exhibited sustained or transient responses to a sustained stimulus. On each of 60 trials, nine probes, arrayed in a 3×3 square centered on the neuron's hotspot (Fig. 1), were simultaneously indented 500 μm into the skin for a duration of 500 ms. Stimuli were interleaved with empty intervals lasting 500 ms.

VARIABLE-DURATION INDENTATIONS. With this protocol, we gauged the extent to which the strength of the OFF response was dependent on the indentation duration. Nine probes, arrayed in a 3×3 square centered on the neuron's hotspot, were indented 500 μm into the skin for a duration of 62, 125, 250, 500, 1,000, or 2,000 ms. Stimuli, each presented 10 times in pseudorandom order, were separated by a 500-ms interval. When this protocol was applied to peripheral afferents, the durations were 60, 80, 100, 120, 160, and 200 ms.

Analysis

ADAPTATION INDEX. RA afferents respond only during the transient portion of an indented stimulus (onset and offset; Fig. 1*B*), whereas SA1 afferents respond during the sustained portion of the stimulus and do not exhibit a distinct OFF response at stimulus offset (Fig. 1*A*). To the extent that cortical neurons receive input from one or the other population of fibers, their responses to sustained indentations should reflect that of one of the two afferent populations. We thus computed, from data obtained in the adaptation protocol, an adaptation index that gauged the strength of the OFF response relative to that of the SUSTAINED response. Because both SA1 and RA afferents produce responses at the onset of the stimulus, we excluded this portion of the response from the analysis, because it does not discriminate between these two populations of afferents. The OFF response, R_{OFF} , was defined as the firing rate evoked during the first 40 ms after stimulus offset, the sustained response, R_{SUSTAIN} , was defined as the firing rate evoked during a 40-ms period beginning 90 ms before the offset of the stimulus (Fig. 1, *top right inset*).² These intervals were adjusted for response latency, defined as the time of steepest rise in the neural response after stimulus onset.³ The baseline firing rate of the neuron was measured from its responses during the 250-ms interval before each stimulus. The index was computed after the baseline firing rate had been subtracted from the stimulus-evoked responses. The values for R_{OFF} and R_{SUSTAIN} were normalized by dividing by their grand mean across the population, as the magnitude of R_{OFF} tended to be an order of magnitude larger than that of R_{SUSTAIN} . The adaptation index, AI , was thus given by

$$AI = \tan^{-1} \left(\frac{|R_{\text{OFF}}|}{R_{\text{SUSTAIN}}} \right) \times \frac{2}{\pi} \quad (1)$$

If a cell was an ideal RA-like neuron, AI would be 1, because the neural response (excluding the ON response and lacking a SUSTAINED

response) was confined to the period immediately after the offset of the stimulus. If a cell were an ideal SA1 neuron, AI would be 0 because the neuron would be silent after the offset of the stimulus. This index yields a perfect dichotomization of SA1 and RA responses at the somatosensory periphery (all SA1 fibers yield an AI near 0, all RA fibers yield an AI near 1; see Figs. 1, *A* and *B*, and 3*A*).

LINEAR MODEL. We determined the extent to which responses of individual cortical neurons to a step indentation could be explained by assuming that responses are a linear function of the peripheral input. In this modeling effort, we used responses to the RF mapping protocol (for reasons described below). Specifically, we computed the peristimulus time histogram (PSTH) of the response of individual cortical neurons to the nine single probe indentations nearest the neuron's hotspot (with 5 repetitions of each; time bin = 1 ms), having verified that the response was relatively consistent over this 1.5×1.5 -mm region (both in magnitude and latency). We computed the mean PSTH of SA1 and RA afferents to the RF mapping protocol. We used responses to the RF mapping protocol rather than to the adaptation protocol because we wished to incorporate into the model the fact that the response latency of the peripheral input varies depending on the position of the stimulus relative to the afferent's RF center (data not shown). Specifically, the farther the stimulus is from the hotspot, the longer the response latency. Thus given that a cortical neuron receives input from afferents whose RFs are spatially distributed, some of the cortical neuron's input (from afferents whose RFs are located under or near the stimulus) is going to arrive at a shorter latency than the rest of the input. This will lead to a temporal smearing of the thalamo-cortical input. For example, the OFF responses of RA afferents are restricted to a very short interval (1–2 ms) when these are stimulated at the center of their RFs (Fig. 1*B*); when OFF responses are averaged over the entire RF, the OFF response is spread over several milliseconds. The PSTH of afferent responses, averaged across all positions within the RF (as measured using the RF-mapping protocol) and across all afferents of each type, constitutes an approximation of this temporally smeared afferent input.

Using the PSTH of the response of a cortical neuron and that of the mean responses of SA1 and RA afferents to the RF-mapping stimuli, we fit the following regression model

$$R_c(t) = \beta_{\text{SA1}} R_{\text{SA1}}(t - \lambda_{\text{SA1}}) + \beta_{\text{RA}} R_{\text{RA}}(t - \lambda_{\text{RA}}) + \beta_0$$

where $R_c(t)$ is the response of a cortical neuron at time t when a single probe is indented at or near its hotspot; $R_{\text{SA1}}(t - \lambda_{\text{SA1}})$, and $R_{\text{RA}}(t - \lambda_{\text{RA}})$ are the mean responses at time t of SA1 and RA afferents, respectively, averaged across position and across afferents (of each type); λ_{SA1} and λ_{RA} are the response latencies for the SA1 and RA afferent input, respectively⁴; β_{SA1} , β_{RA} , and β_0 are regression coefficients. We used standard least squares approach to derive the model parameters (λ_{SA1} , λ_{RA} , β_{SA1} , β_{RA} , β_0).

Having found the combination of parameters that yielded the best fit (as gauged by the coefficient of determination), we performed a linear regression with the optimal values of λ_{SA1} and λ_{RA} and determined whether the coefficients β_{SA1} and β_{RA} were each significantly different from zero using a standard t -test ($\alpha = 0.05$).

RESULTS

We recorded the responses of 19 SA1 afferents, 13 RA afferents, 83 neurons in area 3b, and 132 neurons in area 1. Figure 1 shows the responses of a typical SA1 afferent (*A*), RA afferent (*B*), SA1-like SI neuron (*C*), and RA-like SI neuron (*D*) to a step indentation. The temporal profile of the responses

² We used this interval because it was least liable to be contaminated by the ON response. We used a 40-ms window because the OFF responses were computed over an interval of this duration.

³ We found this to be a robust measure of response latency. To correct for latency, we subtracted the estimated response latency from the time of occurrence of each spike.

⁴ The SA1 and RA responses [$R_{\text{SA1}}(t)$ and $R_{\text{RA}}(t)$] were shifted in time such that their onsets were at time 0; as a result, λ_{SA1} and λ_{RA} represented the veridical latencies of the SA1 and RA input, respectively.

of the two cortical neurons shown in Fig. 1, *C* and *D*, are similar to their peripheral counterparts. Our expectation, based on the segregation of submodalities, was that the large majority of neurons would fall into either the SA1-like or the RA-like category. Many SI neurons, however, exhibited responses such as that shown in Fig. 1*E*: the neuron produced a SUSTAINED response, indicative of SA1 input, as well as a strong OFF response, characteristic of RA input. Figure 2 shows eight other SI neurons that vary in their adaptation properties from SA1-like (*bottom*) to RA-like (*top*), further showing the range of observed responses to step indentations.

Both SA1 and RA fibers produce a strong ON response, so this period in the response of cortical neurons is not indicative of the submodality composition of their input. To assess the degree to which SA1 and RA input impinges on individual neurons in SI, we used the ratio of the magnitude of the OFF response to that of the SUSTAINED response as an index of adaptation (passed through an arctangent function and normalized to 1, see METHODS). This index, *AI*, perfectly dichotomizes peripheral afferents such that SA1 afferents yield values of near 0, whereas RA afferents yield values of near 1 (Fig. 3*A*). According to the submodality segregation hypothesis, values of *AI* derived from cortical neurons would be distributed bimodally with a cluster of values at 0 and another at 1. As seen in Fig. 3*B*, values of the *AI* were bimodally distributed with a peak near 0 and another larger peak near 1; however, many neurons yielded intermediate values of *AI*. Indeed, the *AI*s obtained from 59% of neurons in area 3b and from 58% of neurons in area 1 were between 0.1 and 0.9. The highest *AI* obtained from SA1 afferents was 0.07, and the lowest *AI* obtained from RA afferents was 0.94. The high incidence of intermediate values of *AI* obtained from cortical neurons suggests that many neurons receive convergent input from SA1 and RA afferents.

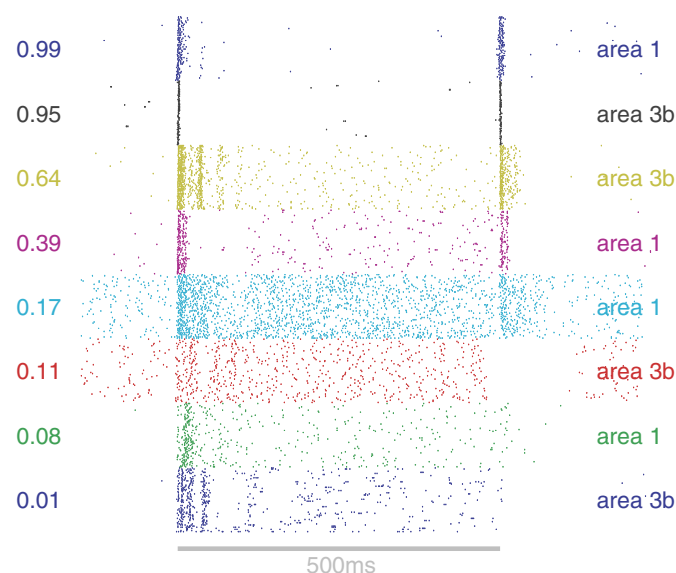


FIG. 2. Responses to step indentations of 8 SI neurons that vary in their adaptation properties, ranging from almost purely SA1-like neurons (*bottom*) to almost purely RA-like neurons. The anatomical location and the adaptation index, *AI*, of the neuron are shown to the right and to the left, respectively, of the corresponding raster. Responses are shifted left (by their latency) so that ON and OFF responses are aligned in the figure.

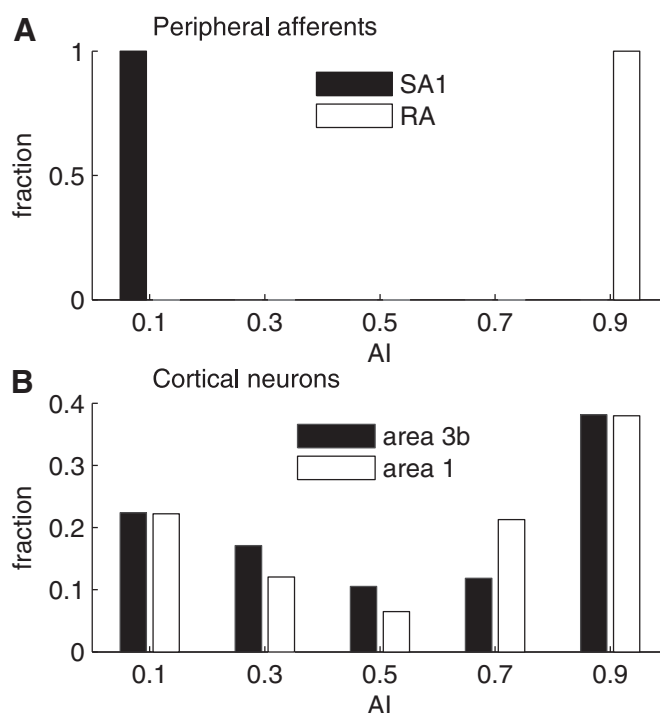


FIG. 3. Distribution of the adaptation index, *AI*, computed from the responses of neurons to step indentations ($N_{SA1} = 19$, $N_{RA} = 13$, $N_{area\ 3b} = 83$, $N_{area\ 1} = 132$). *A*: the index perfectly dichotomizes SA1 and RA afferents such that SA1 afferents yield *AI*s near 0 and RA afferents yield *AI*s near 1. *B*: the distribution of *AI* for cortical neurons is bimodal with peaks near 0 and 1 (with a strong preponderance at the high end). However, most neurons yield intermediate values of *AI*, suggesting that submodality convergence is the rule rather than the exception in SI. Indeed, 59% of neurons in area 3b and 58% of neurons in area 1 yield values of *AI* that fall between 0.1 and 0.9.

To probe the degree to which individual neurons receive SA1 and RA input, we first divided the response to the 500-ms indentation into three periods: the ON period, comprising the first 40 ms of the response, the sustain period, a 300-ms period beginning 150 ms after the onset of the response,⁵ and the OFF period, which comprised a 40-ms interval beginning 500 ms after the onset of the response. For each neuron, we determined whether the responses during the sustained and OFF periods were significantly greater than baseline. Specifically, we compared the spiking rate evoked during the sustained or OFF period to the baseline rate for the 60 presentations of the stimulus (using paired *t*-test with α -value = 0.05). Figure 4 shows the proportion of neurons that produced statistically significant responses in either or both periods. As can be seen, a large proportion of neurons exhibited statistically significant responses during both sustained and OFF periods (51% in area 3b, 40% in area 1), suggesting that these neurons receive input from both SA1 and RA afferents. Furthermore, among unimodal neurons, there were considerably more RA-like than SA1-like neurons in SI.

It is possible that more neurons were classified as RA-like than SA1-like because we have underestimated the SA1 input to many neurons. This underestimation may be because of the type of stimuli used. Indeed, punctate stimuli may not effectively drive the sustained response in these neurons. In auditory cortex, preferred stimuli evoke sustained responses in auditory cortical

⁵ We used a longer period for the SUSTAINED response because the magnitude of this response is much lower than its ON and OFF counterparts.

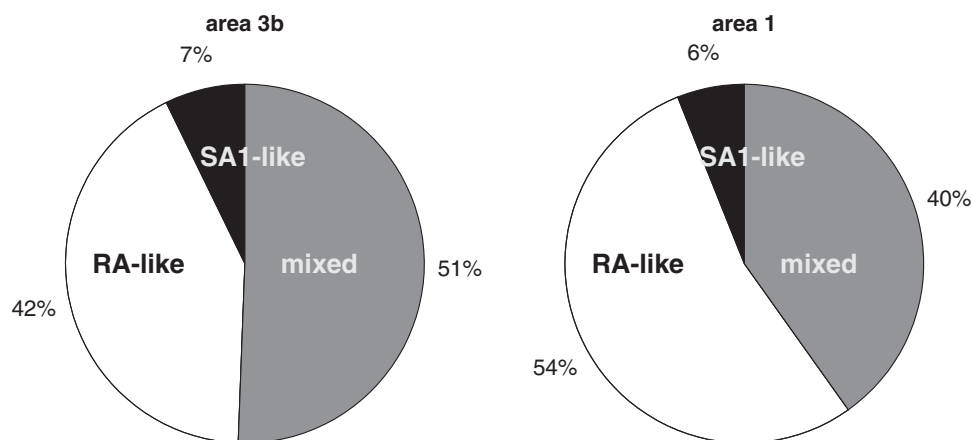


FIG. 4. Proportion of neurons that exhibited a significant SUSTAINED response with no OFF response (SA1-like), neurons that did not exhibit a significant SUSTAINED response but produced a significant OFF response (RA-like), and neurons that exhibited both a significant SUSTAINED and a significant OFF response. Analyses were performed on the responses of cortical neurons to the adaptation protocol, which consisted of 60 presentations of a step indentation lasting 500ms, interleaved with 500-ms silent intervals (see METHODS). This analysis was performed on 83 neurons in area 3b and 132 neurons in area 1.

neurons, whereas nonpreferred stimuli evoke only transient responses at their onset and offset (Wang et al. 2005), a phenomenon that might explain the weakness of the SUSTAINED responses observed in this study.

We have shown in a previous study that the orientation signal conveyed by orientation-selective neurons in areas 3b and 1 is strongest during the SUSTAINED response and weakest during the ON and OFF responses (Bensmaia et al. 2008). We can estimate the extent to which we may have underestimated the SUSTAINED response by comparing the magnitude of the SUSTAINED response of orientation-selective neurons when these are stimulated with indented bars at their preferred and nonpreferred orientations. Figure 5 shows the responses of an SI neuron to bars differing in orientation (from Bensmaia et al. 2008). This neuron's preferred orientation is 67.5° (near vertical). Bars near its preferred orientation evoke a strong SUSTAINED response, whereas bars orthogonal to the preferred orientation evoke only a weak SUSTAINED response. In contrast, the magnitudes of the ON and OFF responses are relatively unaffected by stimulus orientation. We assessed the extent to which neurons produced a SUSTAINED response to bars at their preferred and nonpreferred orientations (using data from Bens-

maia et al. 2008). We found that 46% of orientation-selective neurons produced a significant SUSTAINED response when stimulated at their nonpreferred orientation, whereas 84% of neurons produced a significant SUSTAINED response when stimulated at their preferred orientation, a difference that was statistically significant [$\chi^2(1) = 31.7$, $P < 0.001$]. The incidence of significant SUSTAINED responses to bars in nonselective neurons (52%) was comparable to that of selective neurons when stimulated at their nonpreferred orientation (46%). Thus most neurons seem to receive SA1 input, but this input is obscured when neurons are stimulated using suboptimal stimuli. In other words, the proportions shown in Fig. 4 may underestimate the number of neurons that receive convergent input from SA1 and RA afferents (and accordingly overestimate the incidence of unimodal RA-like neurons). To obtain accurate estimates of the proportions of SA1-like, RA-like, and mixed neurons in SI, it may be important to stimulate these using a wide range of stimuli, thereby increasing the probability of stimulating a neuron with its optimal stimulus.

If indeed the SUSTAINED and OFF responses stem from different peripheral inputs (i.e., according to the convergence hypothesis), the strengths of these two aspects of the response should be uncorrelated. For instance, one neuron may receive strong RA input and weak SA1 input, whereas another might have the reverse pattern of inputs. In contrast, the ON response reflects both SA1 and RA input (Fig. 6, A, D, and G); thus according to the convergence hypothesis, the strength of the ON response should be correlated with the strengths of the SUSTAINED and OFF responses, whereas the magnitudes of the SUSTAINED and OFF responses should be uncorrelated. As shown in Fig. 6, this was indeed the case in area 3b: The partial correlations between the strength of the ON and OFF and ON and SUSTAINED responses were statistically significant ($P < 0.01$; Fig. 6, B and E), whereas the correlation between the magnitudes of the SUSTAINED and OFF responses was not (Fig. 6H). Consistent with the convergence hypothesis, the strengths of the SUSTAINED and OFF responses are uncorrelated because these two response components originate from different populations of afferent fibers. The SUSTAINED and OFF responses were also uncorrelated for neurons in area 1 (Fig. 6I), so results from this anatomical location are compatible with the convergence hypothesis. That the SUSTAINED and ON response were not significantly correlated for area 1 neurons (Fig. 6F) may be because of the fact that the responses of neurons in this area are more nonlinear with respect to the afferent input than are those of

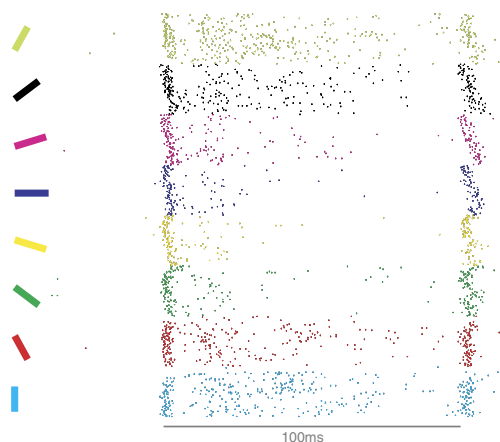


FIG. 5. Responses of a neuron in area 1 to bars at 8 orientations indented into the skin for 100 ms. The rasters of alternating colors denote responses to bars at different orientations (shown to the left of the corresponding rasters). The SUSTAINED response was much stronger when the neuron was stimulated at its preferred orientation than when it was stimulated at the orthogonal orientation. In contrast, the ON and OFF responses were relatively insensitive to orientation. The ON and OFF responses occurred at different latencies because bars at each orientation were indented at different locations within the neuron's RF (see Bensmaia et al. 2008 for details).

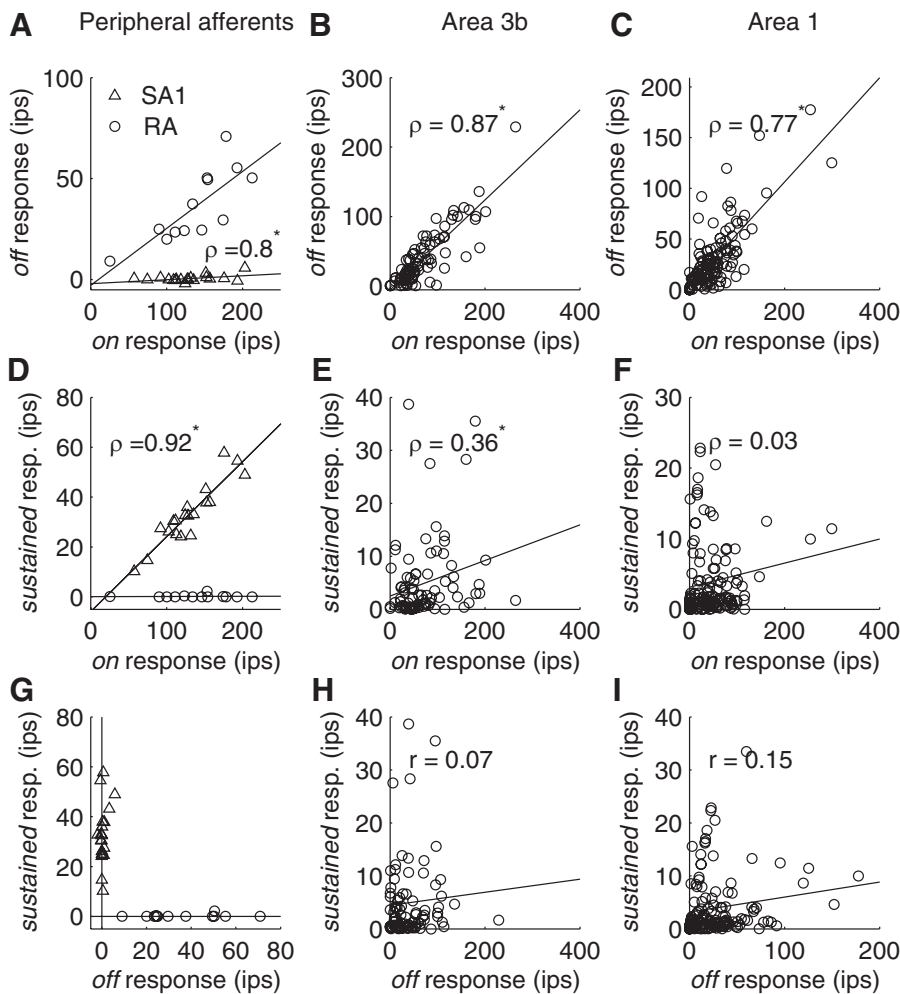


FIG. 6. Interrelationships between the responses evoked during each stimulus interval (ON, SUSTAINED, and OFF; $N_{SA1} = 19$, $N_{RA} = 13$, $N_{area\ 3b} = 83$, $N_{area\ 1} = 132$). **A:** at the somatosensory periphery, the strength of the OFF response of RA afferents is correlated with the strength of their ON response (ρ denotes the partial correlation between the OFF and ON responses, controlling for the SUSTAINED response); **B** and **C:** the magnitude of the OFF response of neurons in areas 3b and 1 is correlated with the magnitude of their ON response. **D:** the strength of the SUSTAINED response of SA1 afferents is correlated with the strength of their ON response (ρ denotes the partial correlation between the SUSTAINED and ON responses, controlling for the OFF response); **E** and **F:** the magnitude of the SUSTAINED and OFF responses of cortical neurons are correlated, particularly in area 3b. **G:** RA afferents do not produce SUSTAINED responses and SA1 afferents do not produce OFF responses. **H** and **I:** as predicted from the convergence hypothesis, the magnitude of the SUSTAINED response of cortical neurons is uncorrelated with that of their OFF response (r denotes the correlation between the SUSTAINED and OFF responses). Asterisks denote significant correlations ($P < 0.01$). At the periphery, the mean ON responses were 129 and 138 ips for SA1 and RA afferents, respectively. The mean SUSTAINED response of SA1 afferents was 33 ips; the mean OFF response of RA afferents was 36 ips. In cortex, the mean ON responses were 62 and 48 ips in areas 3b and 1, respectively. The mean SUSTAINED responses across SA1-like and mixed neurons were 8 and 6 ips in areas 3b and 1, respectively. The mean OFF responses of RA-like and mixed neurons were 43 and 32 ips in areas 3b and 1, respectively.

neurons in area 3b. The increased nonlinearity of area 1 responses with respect to the afferent input is not surprising given that area 1 receives the bulk of its projections not from thalamus but from area 3b (Burton and Fabri 1995; Burton et al. 1995; Jones 1984; Jones and Burton 1976; Jones and Powell 1970; Jones et al. 1982).

Having gathered evidence that many cortical neurons receive convergent input from both SA1 and RA afferents, we wished to quantify the relative contributions of the two populations of fibers to the responses of individual cortical neurons. To that end, we tested a simple linear model, positing that the response of an individual cortical neuron (as the response develops over the stimulus interval) is a linear function of the input it receives from SA1 and RA afferents. As has been found previously (Bensmaia et al. 2008; Sripati et al. 2006), the linear model accounted for a greater proportion of the variance in the responses of neurons in area 3b ($R^2 = 0.80$) than in the responses of neurons in area 1 ($R^2 = 0.73$) (Fig. 7A). To the extent that the neural response comprised an OFF component, the regression coefficient corresponding to the RA input was assigned a nonzero value; to the extent that the neuron produced a SUSTAINED response during the static phase of the stimulus, the SA1 coefficient was nonzero. If the SUSTAINED response dipped below its baseline, the regression coefficient was negative (indicating the SA1 input was inhibitory); a negative RA coefficient would signal a transient dip in the firing rate at the

onset and offset of the stimulus. A major aspect of the temporal response captured by the linear model was the relative strength of the ON and OFF responses. Specifically, to the extent that the relative magnitudes of the ON and OFF responses did not match those of SA1 or RA afferents, the model incorporated both inputs in the prediction. For the vast majority of neurons, the weights assigned to both the SA1 and the RA inputs, β_{SA1} and β_{RA} , were statistically significant. In other words, the temporal profile of the response of individual cortical neurons was

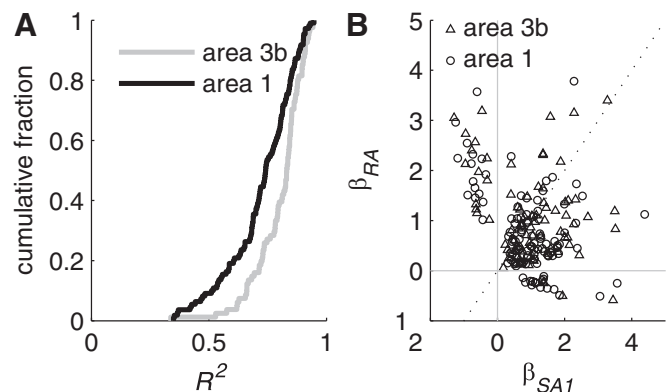


FIG. 7. **A:** distribution of coefficient of determination (R^2) for the fits obtained using the linear model. **B:** fitted regression parameters for SA1 and RA input.

better predicted from a weighted sum of SA1 and RA afferent responses than it was from the responses of a single population of afferents. The preponderance of neurons in area 3b (for which both β_{SA1} and β_{RA} were significant), 85%, received excitatory input from both SA1 and RA afferents; in area 1, 73% of neurons received excitatory input from both SA1 and RA fibers; the remaining neurons in both areas received excitatory input from RA afferents and inhibitory input from SA1 afferents (Fig. 7B).⁶ Importantly, the shallow slope of the function relating the SUSTAINED response to the ON response for area 3b neurons (Fig. 6E) suggests that RA projections to these neurons are stronger than are SA1 projections.

The ratio of $|\beta_{RA}|$ to $|\beta_{SA1}|$ provides an indication of the relative strengths of the SA1 and RA inputs: the mean ratios $|\beta_{RA}|/|\beta_{SA1}|$ were 1.3 and 1 for areas 3b and 1, respectively. In area 3b, the input strength of RA relative to SA1 afferents (1.3) is consistent with the ratio of the RA to SA1 innervation densities on the distal fingerpad, which is also ~ 1.3 (Darian-Smith and Kenins 1980). This near 1 ratio seems inconsistent with the observation that RA input dominates SA1 input in area 3b (based on the slopes of the functions shown in Fig. 6E). We hypothesize that the SUSTAINED response is suppressed when a neuron is stimulated with a suboptimal stimulus (such as a punctate indentation) and enhanced when it is driven by a feature to which it is sensitive (e.g., when an orientation-selective neuron is driven by a bar at its preferred orientation).

An important assumption underlying our analysis is that the OFF response stems from input from RA afferents. An alternative hypothesis is that the OFF response of at least a subset of cortical neurons results from an inhibitory rebound mechanism. One possibility is that these neurons only receive SA1 input. According to this hypothesis, OFF responses result from a rebound from inhibition, triggered by the SA1 response; OFF responses would have a cortical origin and would not indicate RA input. We tested this hypothesis by presenting stimuli of varying duration: Because SA1 afferents adapt during a steady indentation (Bensmaia et al. 2005; Leung et al. 2005), one would expect the magnitude of the rebound to decrease as the SA1 response decreases: as the response decreases, its inhibitory effect also decreases, so the rebound should be reduced. As the duration of the indentation increases, we predicted from the inhibitory rebound hypothesis that the magnitude of the OFF

response would decrease. On the other hand, if the OFF response was caused by a thalamo-cortical volley stemming from RA afferents, its magnitude might either be unaffected by stimulus duration or might increase with increased stimulus duration because of a progressive decay of the inhibition triggered at the onset of the response (DiCarlo and Johnson 2000; Gardner 1984; Gardner and Costanzo 1980; Kyriazi et al. 1994; Sripati et al. 2006). In other words, inhibition may either cause the OFF response (through rebound from inhibition) or suppress it. As shown in Fig. 8B for data obtained from an individual neuron and Fig. 9 for data obtained from the population, an increase in the stimulus duration resulted in a substantial increase in the OFF response of cortical neurons. This increase cannot be accounted for by changes at the sensory periphery as the OFF responses of RA afferents plateaued at short indentation durations (<100 ms; Figs. 8A and 9, magenta trace). When exponential functions were fit to the time course of recovery, the time constants were 202 and 282 ms for neurons in areas 3b and 1, respectively.

DISCUSSION

The main finding of this study is that a large proportion of neurons in SI produce mixed sustained and transient responses, which suggests that they receive input (indirectly through the DCNC and the VPn) from both SA1 and RA afferent fibers. Furthermore, 90% of SI neurons receive some or all of their input from RA afferents (84% or more may receive SA1 input). To characterize the submodality composition of SI neural responses, 1) we assessed the extent to which the response is confined to the transient portions of the stimulus; 2) we determined the extent to which the SUSTAINED and OFF responses are significantly different from baseline; 3) we analyzed the interrelationships between ON, sustained, and OFF responses; and 4) we determined the extent to which the responses of individual SI neurons to step indentations can be accounted for by a linear combination of SA1 and RA responses. We showed that the OFF response increases with indentation duration, which is inconsistent with the hypothesis that it reflects a rebound from inhibition. Our results therefore suggest that many neurons in area 3b receive convergent input from SA1 and RA afferents.

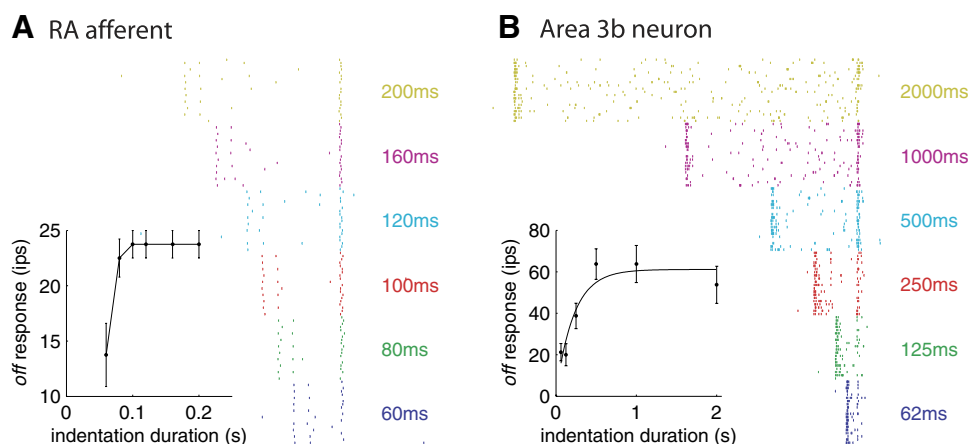


FIG. 8. A: responses of an RA afferent to step indentations varying in duration. Responses are aligned on the onset of the OFF response. The inset shows the magnitude of the OFF response as a function of the indentation duration. The response is stable for indentations that last longer than 62 ms. B: responses of a neuron in area 3b ($AI = 0.52$) to indentations varying in duration. The magnitude of the OFF response was strongly dependent on the indentation duration.

⁶ The SUSTAINED response of these neurons was depressed relative to baseline.

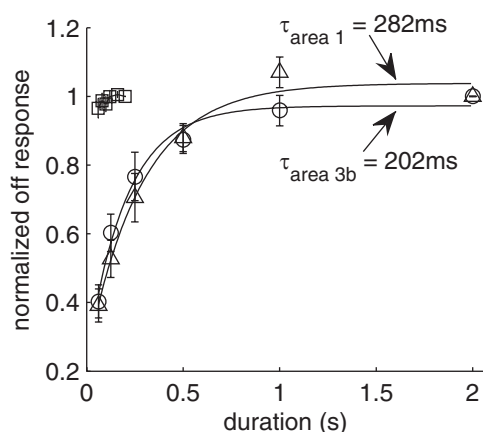


FIG. 9. Magnitude of the OFF response as a function of indentation duration for RA afferents (square), neurons in area 3b (circle), and neurons in area 1 (triangle) ($N_{RA} = 7$, $N_{area\ 3b} = 28$, $N_{area\ 1} = 46$). The OFF response obtained from each neuron for each stimulus duration was normalized by dividing it by the mean OFF response obtained for that neuron at the longest duration tested (250 ms for RA afferents, 2 s for cortical neurons). For all individual neurons in both anatomical areas, the OFF response increased as the indentation duration increased. For RA afferents, indentation duration had little effect on the OFF response for durations > 100 ms.

Effect of indentation duration on the magnitude of the OFF response

As the duration of the indentation increased, the magnitude of the OFF response increased. Indeed, the OFF response evoked by a 2-s indentation was over twice that evoked by a 60-ms indentation. We hypothesize that this increase in the OFF response, itself caused by an RA thalamo-cortical volley, is caused by a progressive recovery from inhibition that is triggered by the neural response, the inhibitory effect decaying over time. The effect of indentation duration on the OFF response has been observed in the responses of neurons in barrel cortex and has been ascribed to synaptically mediated inhibition triggered by the ON response (Kyriazi et al. 1994) in both thalamus (Salt and Eaton 1990) and cortex (Carvell and Simons 1988). Trailing inhibition has also been observed in somatosensory cortex of macaque (DiCarlo and Johnson 2000; Gardner 1984; Gardner and Costanzo 1980; Sripathi et al. 2006) and likely also mediates the progressive increase in the OFF response with increasing indentation duration. Inhibition triggered by a phasic (cutaneous) stimulus has almost completely faded after 80 ms (DiCarlo and Johnson 2000; Gardner 1984; Gardner and Costanzo 1980; Kyriazi et al. 1994; Sripathi et al. 2006), whereas inhibition persists for over 500 ms when triggered by a sustained indentation (Fig. 9). The longer time course of inhibition in the latter case is likely because of the fact that the tonic (SA1-linked) response sustains the inhibition and thus slows its decay. Importantly, inhibition seems to suppress the OFF response rather than cause it, consistent with a thalamo-cortical origin of the OFF response.

Previous studies investigating submodality convergence

Previous studies in primates and cats have shown that submodalities are largely segregated in the DCNC (Douglas et al. 1978; Dykes et al. 1982; Ferrington et al. 1987a,b). However, a proportion of neurons at this early stage of somatosensory processing exhibit response properties that indicate some

degree of submodality convergence (Dykes et al. 1982; Ferrington et al. 1988). In thalamus, submodalities are also largely segregated (Dykes et al. 1981; Jones et al. 1982; Kaas et al. 1984); again, however, some thalamic neurons exhibit responses to vibratory stimuli that suggest that “inputs from several classes of fibers were converging on these cells” (Dykes et al. 1981). These studies suggest that convergence may occur to some degree at early stages of somatosensory processing.

The idea that somatosensory submodalities remain segregated in cortex originates from seminal papers by Mountcastle and colleagues (Mountcastle 1957; Powell and Mountcastle 1959). Mountcastle and colleagues first observed that some neurons only responded to light cutaneous stimulation, whereas others responded only to stimulation of deep tissues (i.e., stimulation of joints or stimulation of deep fascia and connective tissue). The distinction between SA1-like and RA-like neurons in SI was made in a later study and was proposed to reflect input from distinct populations of low-threshold mechanoreceptive afferent fibers (Mountcastle et al. 1969).

In a later study, Paul et al. (1972b) found an approximately equal number of SA1-like and RA-like neurons in area 3b, but an overwhelming prevalence of RA-like neurons in area 1. Hyvärinen and Poranen (1978) found a preponderance of RA-like neurons in SI (76% of the cutaneous neurons) but also observed neurons that exhibited both SA1-like and RA-like properties (20% of the cutaneous neurons), with very few neurons with only SA1-like properties. Finally, Kaas et al. (1981) and Sur et al. (1984) found that only in layer IV did cells exhibit a SUSTAINED response to a step indentation and that neurons in the supra- and infragranular layers exhibited only transient responses. However, most SA1-like neurons also produced OFF responses, suggesting that they received convergent input from both SA1 and RA fibers at the input layer of SI.

Perhaps accounting for some of the divergence in findings, different investigators used different criteria to classify neurons as SA1- or RA-like: in some studies, the distinction was based on the presence or absence of a sustained response to a step indentation (Paul et al. 1972a; Sur et al. 1981, 1984). In other studies, neurons were classified on the basis of their SUSTAINED response and on their ability to produce entrained responses to vibratory stimuli in the high-flutter frequency range (50–100 Hz) (Hyvärinen and Poranen 1978; Mountcastle et al. 1969). We adopted an approach based on the analysis of neural responses to sustained indentations as these evoke dramatically different responses in SA1 and RA afferents. Our approach differed from that of previous investigators in that we interpreted the presence of an OFF response as a marker for RA input. Thus neurons that produced both SUSTAINED and OFF responses were categorized as mixed neurons.

Pacinian representation in SI

PC-like neurons in SI are rare (~6%) but very distinctive in that they have large, poorly defined RFs and are exquisitely sensitive to high-frequency oscillations (Mountcastle et al. 1969). In single-cell recording experiments, PC columns are clustered, typically in area 1 or at the border between areas 3b and 1 (Mountcastle et al. 1969; Paul et al. 1972b). Also, because the PC input is so sensitive relative to input from the other submodalities, it is difficult to ascertain through

hand-mapping alone whether a neuron receives PC input only. None of the neurons tested in this study exhibited PC-like properties.

Cortical columns and the convergence of submodality specific input

Because our neurons were sampled sparsely across the cortical tissue (215 neurons over 5 hemispheres), we cannot directly address the relationships among function, anatomy, and circuitry. However, the prevalence of mixed neurons suggests that convergence may be common in SI. Given that the consensus, as reflected in neuroscience textbooks (Kandel et al. 2000), is that submodalities are isolated in SI, we considered the extent to which our results and conclusions differ from those drawn in earlier studies.

First, submodality convergence is not incompatible with the idea that somatosensory cortex is functionally organized in columns (Mountcastle 1957). It simply suggests that these columns are not unimodal. That individual cortical columns in SI receive convergent input from SA1 and RA fibers may be interpreted as evidence that each column's functional role relies on input from multiple submodalities, which convey information about the relevant aspect of the stimulus. This interpretation of submodality convergence seems discordant with theories postulating that the various populations of mechanoreceptive fibers have different functional roles in tactile perception (Johnson 2001). Indeed, convergence might be interpreted as evidence that most perceptual functions of the somatosensory system (texture perception, form perception, etc.) rely on multiple tactile submodalities (i.e., combinations of SA1, RA, and PC input). For instance, behavioral evidence suggests that the perception of roughness may rely on input from multiple submodalities (Sathian et al. 1989; see Hollins and Bensmaia 2007 for a review).

Our results complement those from previous studies showing that input from one submodality modulates neural responses stemming from another. For instance, PC input has been shown to suppress responses of SI neurons to skin flutter, mediated at the periphery by RA afferents (Tommerdahl et al. 2005; Whitsel et al. 2001, 2003). Superimposing PC input (evoked by high-frequency vibrations) onto RA input (evoked by flutter) leads to a more spatially restricted response in cortex and may thus sharpen spatial information stemming from RA afferents. In fact, some evidence suggests that different modalities may interact at the single cell level in SI. Indeed, some neurons in SI exhibit responses to cutaneous stimulation that are modulated by deep (specifically muscle) stimulation (Zarzecki and Wiggin 1982).

That the preponderance of neurons receives some RA input is surprising. One possibility is that the RA input to mixed neurons does not play a sensory role per se in a subpopulation of neurons. Indeed, RA input may instead switch on a cluster of cortical circuits that analyze information stemming from a specific patch of skin. Because RA fibers respond only to dynamic stimuli, the activated cortical circuits will process information stemming from a body region where a change in stimulation has taken place. A related possibility is that RA input plays a role in directing attention to regions of skin where the stimulus is changing.

A third possibility is that the output of mixed neurons is multiplexed and interpreted differently by different upstream neurons: information about some aspects of the stimulus (e.g., its two-dimensional form) is read out during the sustained portion of the response, whereas information about other aspects of the stimulus is conveyed during its onset and offset. For example, this multiplexing strategy could be adopted in the read-out of the orientation signal conveyed by orientation-selective neurons (Fig. 5). Indeed, orientation information is conveyed during the sustained response and is weakest during the ON and OFF responses (Bensmaia et al. 2008). Perhaps the transient portions of the response (stemming from RA input) convey information about the timing of the stimulus (i.e., its onset and offset), whereas the SUSTAINED response (stemming from SA1 input) conveys information about its spatial properties. Indeed, the evidence suggests that columns that receive a strong RA input may carry a more robust representation of stimulus frequency, a temporal property of the stimulus, than do columns receiving a strong SA1 projection. Indeed, temporally patterned electrical stimulation of RA-like columns yields much better performance than does stimulation of SA1-like columns in a frequency discrimination task (Romo et al. 2000). The multiplexing hypothesis might account for the finding that adapting RA afferents improves spatial acuity (Bensmaia et al. 2006). Indeed, if SA1 and RA input converge onto individual neurons in area 3b, the fine spatial signal carried by SA1 afferents could be contaminated with the less spatially acute signal carried by RA afferents.

Stimulation of each of the three populations of mechanoreceptive afferents yields a distinct sensory experience: pressure for SA1 and flutter for RA, and vibration for PC fibers (Ochoa and Torebjörk 1983). The separability of the sensory experiences evoked by stimulation of the three afferent populations stands in contrast to the large degree of overlap in their central representations.

Distribution of submodality dominance in SI

Sur et al. (1981, 1984) showed that SA and RA neurons in area 3b of primates were segregated in alternating anteroposterior bands within layer IV, an organization analogous to that observed in cats (Dykes and Gabor 1981; Dykes et al. 1980; Sretavan et al. 1983). They proposed that this segregation revealed a functional segregation of two processing streams. As discussed above, however, even "SA" columns seem to receive RA input. Using intrinsic optical imaging, Chen et al. (2001) showed that SA1, RA, and PC input was not homogeneously distributed throughout areas 3b; instead, preferential activation of each of the three populations yielded a different topographical pattern of activation.⁷ Importantly, however, there was a large degree of overlap between the patterns of activation evoked by the three populations of afferents. Similar results were shown in area 1 (Friedman et al. 2004). Thus to the extent that there exists functional segregation in SI, it does not seem to strictly follow submodality lines.

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⁷ They also obtained very different results depending on the anesthetic they used, an important result in interpreting findings from early studies of submodality segregation in SI in which anesthesia was used.

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