Simultaneous encoding of tactile information by three primate cortical areas

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We used simultaneous multi-site neural ensemble recordings to investigate the representation of tactile information in three areas of the primate somatosensory cortex (areas 3b, SII and 2). Small neural ensembles (30–40 neurons) of broadly tuned somatosensory neurons were able to identify correctly the location of a single tactile stimulus on a single trial, almost simultaneously. Furthermore, each of these cortical areas could use different combinations of encoding strategies, such as mean firing rate (areas 3b and 2) or temporal patterns of ensemble firing (area SII), to represent the location of a tactile stimulus. Based on these results, we propose that ensembles of broadly tuned neurons, located in three distinct areas of the primate somatosensory cortex, obtain information about the location of a tactile stimulus almost concurrently.

One of the most basic functions of the nervous system is the localization of sensory stimuli. Information about stimulus location is, of course, available in the peripheral receptor array, whose activity may be processed along divergent paths and levels of central pathways. For instance, the translation of this receptor activity through the thalamocortical circuitry may produce a sensation of localization, whereas translation of the same activity through the spinal circuitry may produce a reflex movement toward or away from the stimulus location. How might the brain actually combine information available in many neural structures to produce a perceptual indication of the location of a tactile stimulus? In the complex somatosensory system of primates, which includes many reciprocally connected cortical areas[1], a fundamental question is whether information about tactile stimulus localization is preserved throughout these many cortical areas, or whether such information is conserved within particular cortical populations that then serve as a general reference. This second alternative seems to be suggested by the degradation of topographic maps of body surface as one proceeds from early to late stages of cortical processing[1]. Clearly, information about stimulus location is well preserved in the precise topographic maps in the brainstem, thalamus and primary somatosensory cortex. Yet, is this information necessarily lost in other cortical areas where neurons have large receptive fields? An alternative possibility is that information about stimulus location could be transformed from a spatial code, easily recognized at a single-neuron level, to a distributed code, best recognized in the simultaneous activities of large populations of cortical neurons. It is also conceivable that at late stages of cortical processing, the location of a stimulus could be represented in the temporal patterns of neural ensemble firing. In fact, research on artificial neural networks demonstrated that a 'temporal encoding' strategy emerges as a signature of recurrent distributed systems that can resolve noisy patterns[2–4]. This temporal coding could manifest itself through precise sequences of action potentials, synchronous neuronal firing or time-dependent modulation of the neural ensemble firing rate.

Such issues are fundamental to our understanding of how the primate cerebral cortex operates and are not restricted to the special functions of the somatosensory system. In the auditory cortex, for instance, the lack of an obvious spatial map for sound location has led some to propose that populations of auditory cortical neurons may encode location in a complex distributed fashion that does not depend on precise spatial mapping at the single-neuron level[5]. To date, however, little attention has been paid to the possibility that such nonspatial codes could effectively represent tactile stimulus location in the somatosensory system. Indeed, the secondary somatosensory cortex and fields of the posterior parietal cortex have long been considered to be uninvolved in stimulus location coding, because the large receptive fields of neurons in these regions[1] would seem to preclude the accurate representation of this information. This view could be challenged by evidence that accurate stimulus location information can be extracted from the collective responses of neural ensembles in these cortical areas, as proposed by distributed models of cortical function[6–12].

To address this possibility, in this study we used large-scale, chronic, multi-site neural ensemble electrophysiology[13,14] to simultaneously record the sensory responses of up to 135 single neurons located in three cortical somatosensory areas (areas 3b,

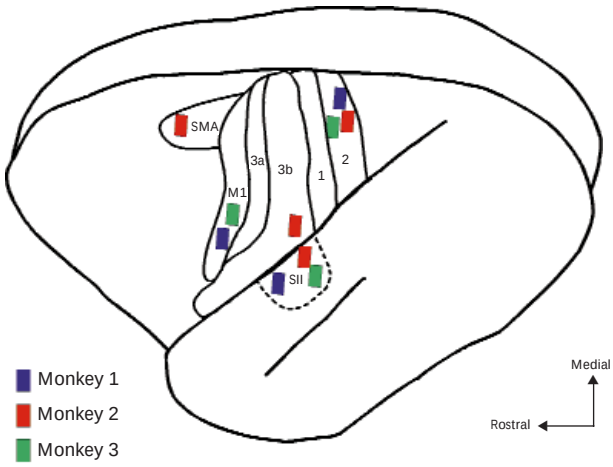

Fig. 1. Location of chronically implanted microwire arrays used to record neuronal ensemble activity in the somatosensory and motor cortex. In this schematic representation of the somatosensory and motor areas of the neocortex of the owl monkey, each colored rectangle depicts the anatomical location of a chronically implanted array containing 16 microwires (organized in two rows of eight). Note that SII is buried within the lateral sulcus.

SII and 2) in adult owl monkeys (*Aotus trivirgatus*)[15–17]. This species was chosen because the cortical areas of interest are accessible on the dorsal surface of a relatively smooth neocortex, and much is known about the organization and connections of its cortex[15].

Results

In each of the three monkeys used in this study, about 80% of the microwires yielded at least one discriminable single unit, and up to four neurons per electrode could be discriminated in each animal. Chronically implanted microwire arrays provided stable neural population recordings for 8 months in monkey 1, 19 months in monkey 2 and 5 months in monkey 3. During these recording periods, a maximum of 135 (monkey 1, 48 microwires), 104 (monkey 2, 48 microwires) and 77 (monkey 3, 32 microwires) cortical neurons were simultaneously discriminated in a single recording session. Different samples of neurons were obtained in each recording session, although a given sample of neurons was often kept for many days. Histological analysis showed that the neurons recorded in this study were located primarily in the infragranular layers of the following cortical areas (Fig. 1): for monkey 1, primary motor cortex (MI), secondary somatosensory cortex (SII) and posterior parietal area 2; for monkey 2, supplementary motor area (SMA), area 3b, SII and area 2; and for monkey 3, MI, SII and area 2. Only results from the somatosensory areas 3b, SII and 2 are discussed here.

Broadly tuned neuronal responses to tactile stimulation were observed in the infragranular layers of the primate somatosensory cortex (Fig. 2). Raster plots and corresponding post-stimulus time histograms (PSTHs) were used to depict the sensory responses of a sample (6 out of 30) of simultaneously-recorded SII neurons following the stimulation of different hand locations. As a rule, individual SII as well as area 2 neurons responded to the stimulation of multiple digits and regions of the dorsal surface of the hand (Fig. 3). Quantitative analysis of PSTHs in both awake and lightly ketamine-anesthetized (10–15 mg/ kg) animals demonstrated that virtually all neurons in the infragranular layers of areas SII and 2 showed large multi-digit receptive fields (RFs). These RFs were considerably larger than those observed in layer IV of area 3b, and similar to the large neuronal RFs previously reported in rhesus monkeys[16,17]. The raster plots (Fig. 2) also illustrate the difficulty of identifying which skin site was stimulated when only a single trial of single neuron's response was considered (see neurons 22a, 25 or 30a, for instance). In fact, for most neurons, the location of the stimulus could not be identified by examining either single-trial sensory responses or averaged information from many trials depicted in PSTHs (Fig. 2). In addition, the areal location of a cortical neuron could not be established by simple inspection of individual neuronal PSTHs (Fig. 3). This is because most somatosensory cortical neurons showed similar averaged sensory responses that could not be distinguished in terms of minimal latency, duration or frequency of responses. This similarity in intrinsic temporal response characteristics of somatosensory neurons is illustrated by the comparison of a sample of simultaneously recorded SII and area 2 neurons, which showed virtually identical PSTHs in response to punctate tactile stimulation (Fig. 3).

In general, the multidigit RFs of SII and area 2 cortical neurons were characterized by the presence of a center whose stimulation elicited the largest sensory response and the shortest response latency. Stimulation of surround regions of the RF induced smaller but statistically significant excitatory responses at longer response latencies, as previously reported in rats[18]. In addition to having multi-digit RFs, area 2 neurons could be driven by stimulation of the face and the back of the hand (Fig. 4c and d). By combining the sensory responses of individual neurons into population maps, we were able to reconstruct the neural ensemble representations of punctate tactile stimuli across the somatosensory cortical areas (Fig. 4) in the same animals. Punctate stimulation of different parts of the hand and/or face produced distinct spatiotemporal patterns of neuronal activation in SII (Fig. 4a and b) and area 2 (Fig. 4c and d). These distinct profiles were generated by variations in the response magnitude and latency of individual neuronal sensory responses. Note, however, that many neurons contributed to the population response resulting from a given tactile stimulus, suggesting that distributed representations exist in areas SII and 2 of the primate somatosensory cortex.

Further analysis of the population maps for all three cortical areas recorded in each animal revealed a considerable latency overlap between the sensory responses of neurons (measured with 1-ms accuracy). In an example recording (Fig. 5a), this activity overlap was observed during stimulation of the tip of the D2 digit in monkey 3. This stimulus initially triggered a sensory response in neurons located in SII (10–15 ms), and a couple of milliseconds later massive neural firing was observed in both SII and area 2. Comparison of minimal response latencies for all neurons recorded in areas 3b, SII and 2 (Fig. 5b) revealed a significant degree of overlap.

Ensemble coding of tactile stimulus location

Our overall strategy in this analysis was to measure how well the firing patterns of cortical ensembles could predict, on a single trial, the location of a punctate tactile stimulus applied to the animal's body. Because many skin sites were stimulated in random order, multiple combinations involving 3, 5 or 10 sites were used for this analysis. Ten-fold cross-validation was employed for each analysis to yield the highest stability and accuracy of the results. For each combination of sites, 10% to 90% of the original

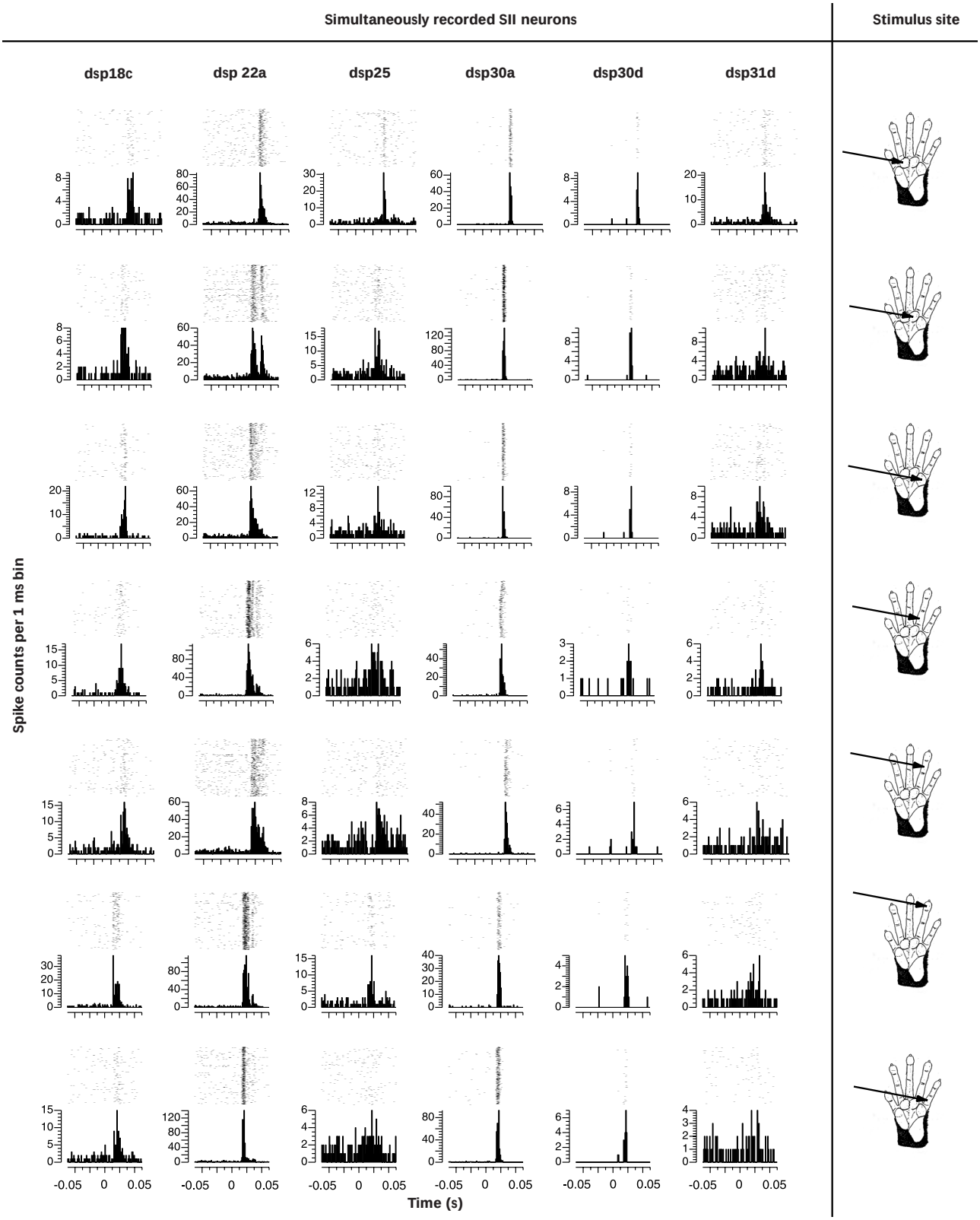

Fig. 2. Single-neuron responses to tactile stimulation at different sites on the hand. Raster plots and post-stimulus time histograms were used to illustrate the sensory responses of a subset of simultaneously recorded SII neurons following the punctate tactile stimulation of seven neighboring regions of the monkey hand. All single SII neurons (identified on top of each column) tended to respond significantly to all the stimulated skin sites. In addition, each neuron's averaged responses (see histograms) were similar across these skin sites. Inspection of single trial responses for a given single neuron did not allow identification of the site of stimulation, either because the response was indistinguishable to that obtained for other sites or because the neuron did not fire in that trial.

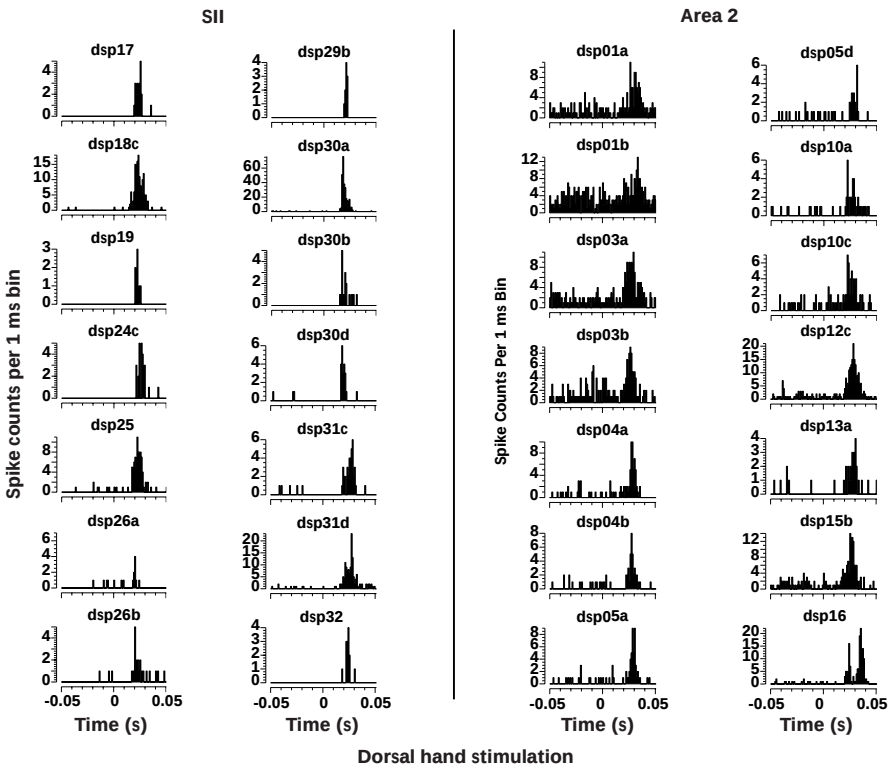

Fig. 3. Post-stimulus time histograms depict the simultaneously recorded sensory responses of ensembles of neurons in areas SII and 2 following the punctate tactile stimulation of hair located in the dorsal hand of a monkey. Notice that all neurons in these two areas responded to this stimulus (as well as stimulation of many other sites, not shown). Inspection of these and other histograms did not reveal any clear encoding strategy. For instance, no difference in the frequency of response can be observed between SII and area 2 neurons. Moreover, both populations showed overlapping minimal response latencies. Finally, the duration of the single-neuron sensory responses in both areas was similar. Therefore, no difference in intrinsic temporal response characteristics between these two populations of neurons was observed in these post-stimulus time histograms.

360 stimulus trials obtained per skin site were used to 'train' different artificial neural networks or to derive discriminant functions using linear discriminant analysis. Once the training phase was completed, the trained artificial networks (or the discriminant functions, in the case of linear discriminant analysis) were used to identify which of the skin sites was stimulated in each of the remaining 'testing' trials. Testing trials were never presented during the training phase of the analysis. Both testing and training trials were presented in a random sequence, and equal numbers of trials per site were used.

As a way to cross-validate our results, different analysis parameters were varied. First, three methods for statistical pattern recognition (linear discriminant analysis, learning vector quantization and back-propagation) were applied to the same data

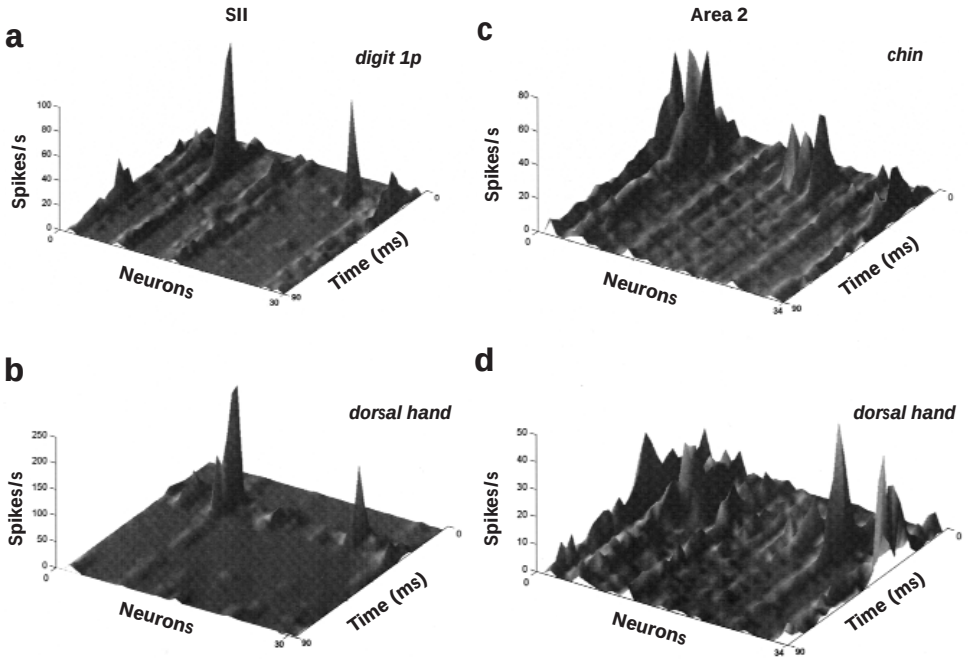

Fig. 4. Distributed responses of area SII and 2 neural ensembles. Population maps depict the simultaneously recorded sensory responses of neural ensembles located in areas SII and 2 of the owl monkey somatosensory cortex. **(a, b)** Stimulation of the proximal phalanx of digit 1 and of the dorsal surface of the hand elicit distinct spatiotemporal patterns of response in the SII cortex. **(c, d)** Stimulation of the face and dorsal surface of the hand elicit distinct spatiotemporal patterns of ensemble activity in area 2. In each of the three-dimensional plots, the *x*-axis depicts the simultaneously recorded neurons, the *y*-axis is post-stimulus time in milliseconds, and the *z*-axis is the response magnitude in spikes per second.

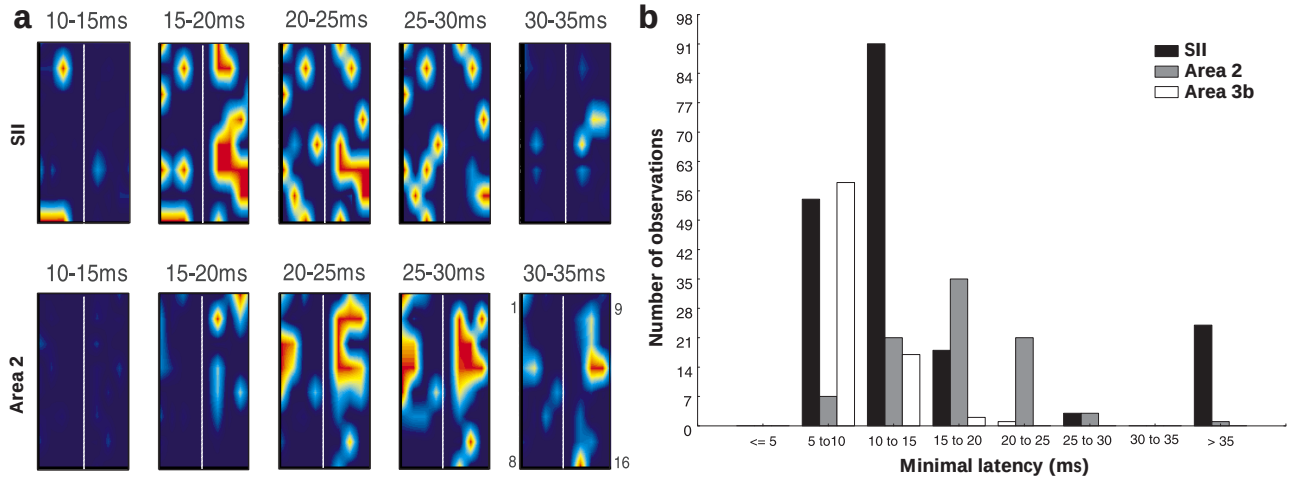

Fig. 5. Concurrent activation of somatosensory cortical areas following punctate tactile stimulation. **(a)** Color-coded three-dimensional matrices depict the post-stimulus firing of simultaneously recorded neurons in the SII cortex (top panel) and area 2 (bottom panel) following the stimulation of a finger tip. These plots depict the response of each neuron according to its position in the 2 X 8 electrode arrays implanted in the two cortical areas. Data were plotted at 5 millisecond post-stimulus time intervals. At each time epoch, the two rectangular panels, separated by a vertical white line, were used to represent the spatial extent of neural activity. The *y*-axis of each rectangular panel represents the rostrocaudal position of the microwires (top rostral-most electrodes 1 and 9; caudal-most wires 8 and 16), the left rectangle depicts the lateral component of the array, and the right panel depicts the medial component of the array. Because up to four neurons were recorded per microwire, the *x*-axis of each rectangle contains up to four slots per microwire to represent the response of each of the recorded neurons. The *z*-axis represents variations in neuronal response magnitude (dark red represents >4 standard deviations above spontaneous firing, and blue represents spontaneous firing, in spikes per second). Notice that following a small activation of the SII cortex at the 10–15-ms epoch, there is concurrent activation of both cortical areas (SII and 2). **(b)** Minimal latency distributions for single neurons in each of the three cortical areas. The minimal latencies calculated for data obtained in two monkeys demonstrate that following an initial activation of both area 3b (minimal response latency, 9.0 ± 2.2 ms) and SII (12.5 ± 3.52 ms), concurrent activation was observed in these areas and area 2 (minimal response latency, 17.8 ± 5.0 ms).

sets. Second, three unique formats of data input were used for each pattern recognition analysis: raw spike trains, principal components[19] and independent components[20] derived from the raw spike trains. Finally, different training-set sizes (90%, 50% and 25% of the total number of trials) were used in the analysis. Through all of these variations in analytical approach, statistically similar results were obtained (Fig. 6a and b), indicating that neither the pattern recognition analysis method (Fig. 6a, $p < 0.77$, MANOVA), nor the type of data preprocessing, nor the training schedule influenced the final outcome of the population analysis. The relative proportion of training to testing trials was also generally unimportant for these results, although significant reductions in discrimination performance by the artificial neural networks were obtained when the number of training trials was reduced to 10% of the total ($p < 0.03$, Fig. 6b).

An artificial neural network based on learning vector quantization was used to evaluate the discrimination capabilities of simultaneously recorded cortical neural ensembles located in areas 3b and SII (monkey 2, Fig. 7a and b) and areas SII and 2 (monkey 3, Fig. 7c and d). A total of 4 (monkey 1), 10 (monkey 2) and 25 (monkey 3) unique combinations of 3 skin sites were used to quantify each cortical ensemble's discrimination capability. This analysis revealed that, when independently tested, statistically significant single-trial discrimination of the location of a tactile was achieved using cortical ensemble firing patterns from each of the three areas investigated (3b, SII and area 2) and a variety of skin site combinations. For example, the firing pattern of an ensemble of 24 neurons located in area 3b of monkey 2 uniquely specified the correct identification of the stimulus location in 72.5 ± 3.5% of the individual testing trials (Fig. 7a and b). The same analysis revealed that SII ensembles provided the correct identification of the stimulus location in 94.5 ± 0.6% of the single testing trials in monkey 1 (40 neurons, not shown), 70.0 ± 1.9% of the trials in monkey 2 (26 neurons, Fig. 7a and b) and 73.3 ± 1.6% in monkey 3 (30 neurons, Fig. 7c and d). Above-chance discrimination was also obtained when area 2 ensembles (48.0 ± 1.8%, 34 neurons, monkey 3, Fig. 7c and d) were tested independently.

The potential encoding mechanisms used by each cortical area were investigated by, first, sequentially removing neurons ('neuron dropping') from each cortical ensemble to measure the variation in discrimination capability as a function of the ensemble size; second, independently shuffling the trial order for each neuron, a maneuver aimed at testing the robustness of intertrial neuronal correlations; and third, varying the integration time used to describe each neuron's sensory response (from 3 to 45 ms), a procedure that altered the temporal structure of each neuron's sensory response ('bin clumping').

The neuron-dropping procedure further supported the existence of distributed representations of tactile information in each of the three cortical areas, by demonstrating that removal of individual 'best predictor' neurons from the ensemble produced only small and gradual reductions in the correct classification of single trials by the neural ensemble, as shown for four neural ensembles (Fig. 8a and b). SII functions (from two monkeys) were very similar to each other but differed when compared to those obtained for areas 3b and 2 ensembles. Even though area 3b ensembles outperformed area 2 populations of the same sizes,

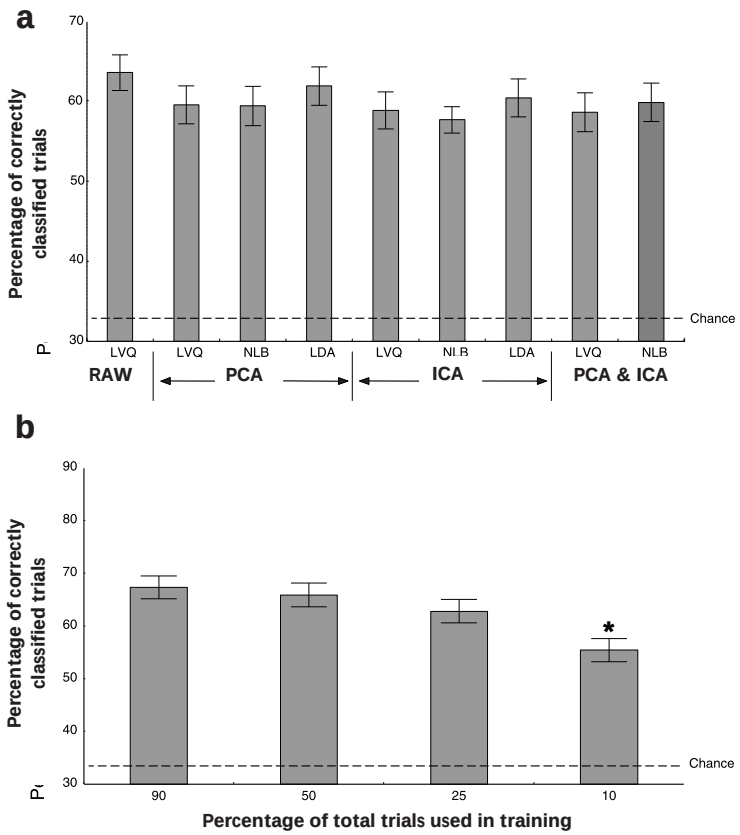

Fig. 6. Multiple statistical pattern recognition approaches cross-validate results of neural ensemble performances. **(a)** Use of three pattern recognition algorithms (learning vector quantization, non-linear back-propagation network and linear discrimination analysis) and three types of data input format (raw spike data, principal component, PCA, and independent components, ICA) produced similar results ($p < 0.77$, MANOVA). **(b)** Similarly, no statistical difference was observed when 25–90% of the trials were used to train the artificial networks (learning vector quantization, LVQ, and back propagation, NLB) and derive the discrimination functions (linear discriminant analysis, LDA). Because statistically significant reductions in discrimination could occur when only 10% of the trials were used, this training routine was avoided.

the two cortical areas showed very similar gradual decays in single-trial discrimination performance as neurons were removed from the ensembles. Increasing the number of skin sites used in the analysis (from 3 to 10 sites) reduced discrimination performance. However, above-chance discrimination was observed for each combination of sites. Overall, most individual neurons alone were poor discriminators of the stimulus location on a single trial, as the vast majority of the single 3b (92%), SII (96%) or area 2 (100%) neurons tested could not be used to classify more than 50% of the trials correctly for combinations of 3 skin sites.

Independent shuffling of trial order for each single neuron had little effect on the overall classification of single trials by either artificial neural networks or linear discrimination analysis. This suggested that the neuronal responses were tightly locked to the presentation of the tactile stimuli throughout the duration of each recording session. In some cases, the performance of artificial neural networks improved slightly for certain skin site combinations after trial shuffling, which could suggest the existence of correlated 'biological noise' embedded in the single-neuron responses on each trial. Furthermore, this finding suggests that effective single trial discrimination of punctate tactile stimulus location does not require precise (1–2 ms accuracy) intra-trial neural ensemble spiking sequences[21,22], extensive neuronal synchronization[23] or covariance across the population of simultaneously recorded neurons.

DIFFERENCES IN ENCODING STRATEGY BETWEEN CORTICAL AREAS

Both temporal- and rate-based codes[24] have been proposed to account for the ability of cortical neural ensembles to represent sensory information. In the final step of our analysis, we investigated which of these encoding schemes could best explain the single-trial representation of tactile stimuli in the somatosensory areas 3b, SII and 2. First, we studied whether the temporal structures of the sensory responses of neurons in each cortical area were involved in the encoding of stimulus location. To address this issue, we examined the artificial neural network's ability to classify correctly the location of a stimulus on a single trial using bin clumping, by integrating neuronal firing data into a range of bin sizes (from 15 3-ms time bins to a single 45-ms bin) used to represent the first 45 ms of post-stimulus period, as shown for pairs of cortical areas recorded in two monkeys (2 and 3; Fig. 9). Bin clumping significantly reduced the discrimination capability of SII neural ensembles in all three monkeys: from 94.5 ± 0.6% to 90.3 ± 1.1% in monkey 1 (not shown), from 70.0 ± 1.9% to 61.2 ± 2.1% in monkey 2 ($p < 0.001$; Fig. 9a) and from 73.3 ± 1.6% to 59.5 ± 1.7% in monkey 3 ($p < 0.0001$; Fig. 9b). Bin clumping, however, had no effect on the discrimination capability of the 3b ensemble in monkey 2 (72.5 ± 3.5% using 3-ms bins and 72.0 ± 3.7% using a single 45-ms bin, $p < 0.8$; Fig. 9c) or the area 2 ensemble recorded in monkey 3 (48.0 ± 1.8% using 3-ms bins and 48.7 ± 1.5% using a single 45-ms bin, $p < 0.72$; Fig. 9d). Even though single SII neurons have been reported to respond well to time-varying stimuli, particularly high-frequency vibrotactile stimuli[25], no basic differences in intrinsic temporal response characteristics were observed in the present study between SII neurons and neurons recorded simultaneously in either areas 3b or 2. (See Fig. 3 for a comparison between areas SII and 2.) A plausible interpretation of these bin-clumping results is that the reduction in single trial discrimination by SII ensembles resulted from the disruption of time-dependent patterns of neur-

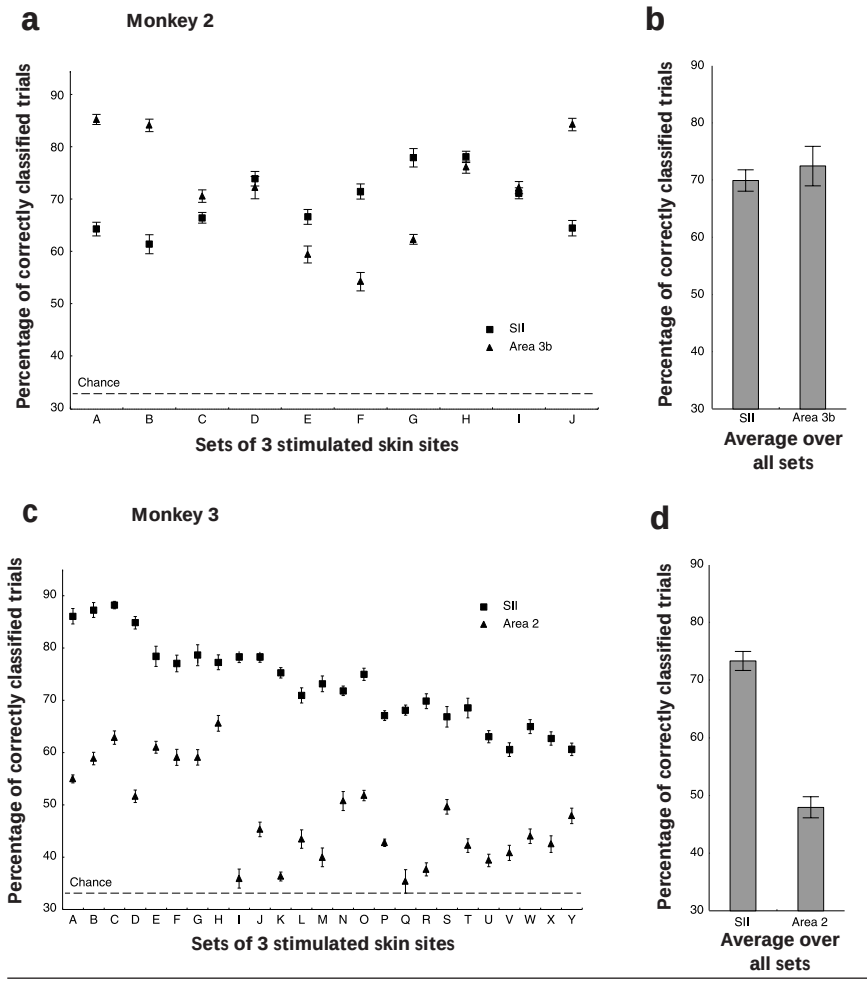

Fig. 7. Single-trial discrimination by neural ensembles located in three somatosensory cortical areas (3b, SII and area 2) as measured by an artificial neural network trained with a learning vector quantization algorithm. **(a)** Neural ensembles in areas 3b and SII (monkey 2) performed at higher-than-chance levels in discriminating the location of punctate tactile stimuli from different combinations of three skin sites. **(b)** When the results obtained for all skin site combinations were averaged, 72.5% of the single trials were correctly classified using area 3b neurons, whereas 70% of the single trials were correctly classified with SII neurons. **(c, d)** Performance of neural ensembles located in areas SII and 2 in monkey 3. Although neural ensembles in both areas SII and 2 (monkey 3) showed higher-than-chance performance, SII ensemble showed a much higher level of discrimination (73.3%) on average than area 2 (48%, $p < 0.001$).

al ensemble firing (on the order of 10–15 ms). Because bin clumping did not affect the trial classification accomplished by using area 3b and 2 neurons, these results raise the hypothesis that ensembles of cortical neurons may achieve the same computational goal (in this case identifying the stimulus location) by using different encoding strategies. Thus, coding of stimulus location in the SII cortex could use the temporal structure of its neuronal population sensory responses, whereas areas 3b and 2

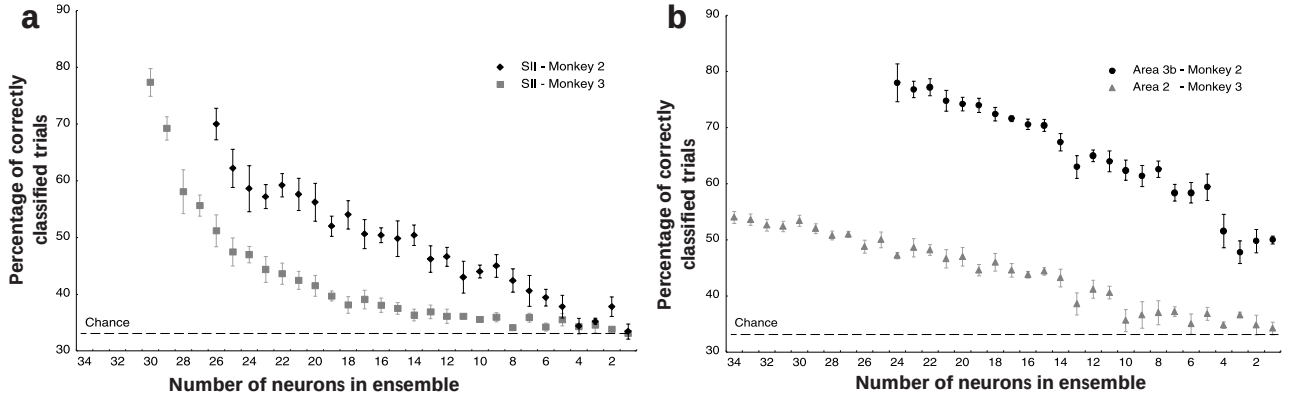

Fig. 8. For all three cortical areas analyzed (3b, SII and 2), the single-trial discrimination capability varied as a function of the ensemble size. Shown here are the effects of sequential removal of the best predictor neurons from the population (neuron dropping) on single-trial discrimination of the stimulus location. **(a)** Neuron dropping in two SII ensembles (from monkeys 2 and 3) resulted in similar trends of decay in single-trial discrimination ability (percent correct). Notice that when the SII ensembles were reduced to about five neurons, the performance was close to chance (33%). **(b)** Neuron dropping in areas 3b and 2. The curves depict the discrimination ability as a function of neural ensemble size for these areas. Graceful decay in discrimination performance also occurred as a result of decreasing ensemble size.

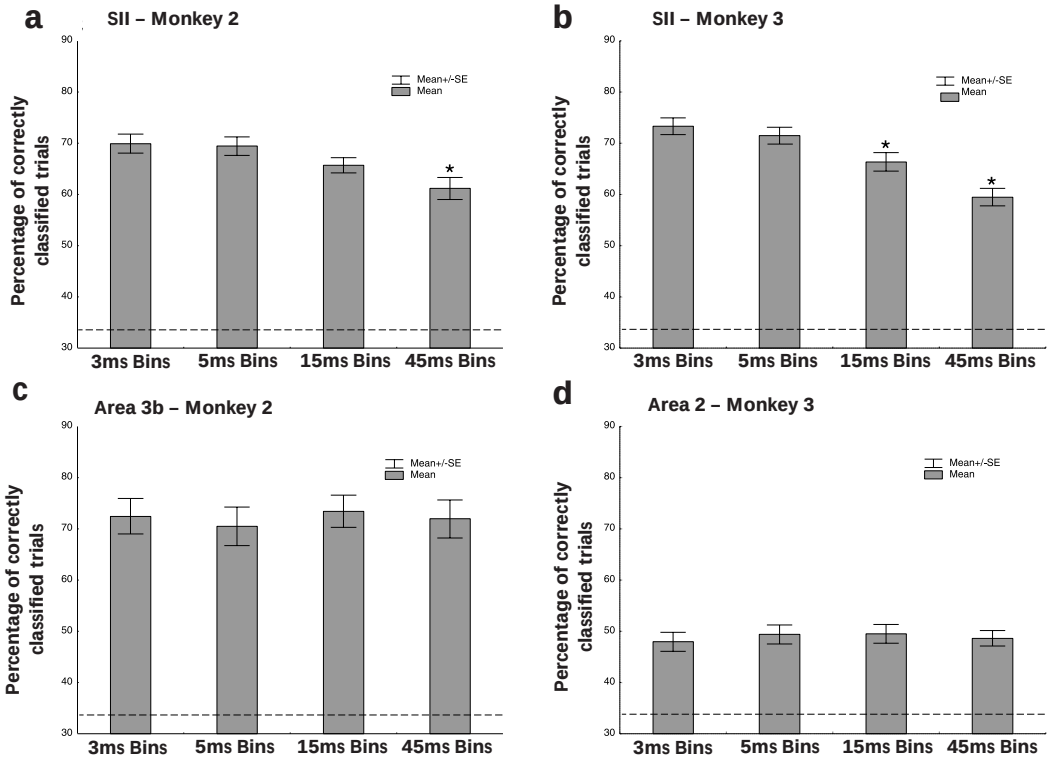

Fig. 9. The effect of bin clumping on the discrimination capability of cortical areas. Whereas a significant reduction in discrimination capability was observed when bin clumping (that is, increasing the size of the bin describing neuronal firing from 3 to 45 ms) was applied to SII neural ensembles in monkeys 2 (a) and 3 (b), no effect was observed either in area 3b (c, monkey 2) or 2 (d, monkey 3) neural ensembles. These results suggest that the temporal structure of population responses could be more fundamental for encoding the location of a tactile stimulus in area SII than in the other two somatosensory cortical areas.

could encode the same stimulus locations by simply using variations in the mean ensemble firing rate. Moreover, our results suggest that SII contains the requisite information for coexistence of both temporal and rate coding schemes because above-chance discrimination was observed for the SII cortex of all three monkeys after the temporal structure of neuronal sensory responses were eliminated by bin clumping. Therefore, a residual rate code could still be sufficient for ensembles of SII neurons to compute the location of a tactile stimulus on a single trial.

As described above (Fig. 5b), distributions depicting the minimal response latency for neurons located in three parietal cortical areas showed a great deal of overlap at about 10 to 15 ms after the stimulus delivery. However, neurons located in all cortical areas also exhibited long-latency responses (15–45 ms). By independently testing the contribution of three consecutive 15 ms bins (0–15, 15–30 and 30–45 ms) on the discrimination capability of each cortical area, we observed that the highest single-trial discrimination performance was obtained when we analyzed neural responses in the interval from 0 to 30 ms in areas 3b and SII and in the interval from 15 to 45 ms for area 2. These results provided further support for the notion that the many cortical areas that constitute the primate somatosensory cortex could operate almost simultaneously to compute the location of a given stimulus.

Discussion

The results described here demonstrate that the spatiotemporal firing patterns of neural ensembles, formed by broadly-tuned neurons and located in three cortical areas of the primate somatosensory cortex, contain enough information to specify the location of punctate tactile stimuli on a single trial. This study also provides the first compelling evidence that cortical areas could carry out such computations almost simultaneously, but using different representational strategies (that is, temporal versus rate coding or a combination of both schemes) to achieve the same goal. In particular, the spatiotemporal character of neuronal responses in the SII cortex was shown to contain the requisite information for the encoding of stimulus location using temporally patterned spike sequences, whereas the simultaneously recorded neuronal responses in areas 3b and 2 contained the requisite information for rate coding.

Based on our results, we hypothesize that information-processing strategies may vary across cortical areas of the primate somatosensory system but that these areas may still act collectively to encode a variety of stimulus attributes. In support of this possibility, processing of sensory information in the primate brain involves interactions between dozens of cortical areas, each of which is interconnected with a number of other areas[1,26–28]. In the last few years, this distributed connectivity scheme has provided the basis for a new theoretical framework for cortical function, which departs from the notion that each cortical area is dedicated to one specific task and contains highly specialized, feature-detector neurons. The alternative notion suggests that single cortical areas, and the neurons within them, participate in a variety of functions and that they interact extensively[6–12]. This model of cortical function incorporates the benefits of population coding in distributed networks[2–4,12] and implies that a large

number of neurons is involved in any particular perceptual or motor task[9,11,21]. Therefore, the fundamental focus of cortical computation shifts from the single neuron toward interconnected neural ensembles as originally proposed by Hebb[6,29].

Therefore we envision that neural populations located in different cortical areas could either share the same type of information or cooperate to improve their individual performance. Moreover, the finding that information about the location of a tactile stimulus could be readily extracted from all three cortical areas suggests that these fields may collaborate in the definition of a unified perceptual experience of the stimulus location. Cortical areas could also use the information about stimulus location to produce unique computations or to relate their outputs to a precise representation of the stimulus location. In a more general sense, our results raise the possibility that cortical areas, although specialized to differing degrees, could process multiple attributes of a sensory stimulus simultaneously. Thus, by using combinations of encoding mechanisms (temporal versus rate coding), populations of neurons could 'multiplex' various types of information in their firing patterns[30,31]. According to this scheme, single neurons would likely participate in multiple coexistent representations within each cortical area. Paradoxically, however, their individual firing patterns would not reliably encode any of the stimulus features on a single trial. We acknowledge that, in this model of cortical function, there is no strict requirement for a specific binding mechanism, such as synchronous neuronal activity[23], although such a mechanism may be involved in other aspects of sensorimotor processing besides identifying stimulus location. In our model, information regarding the tactile stimulus location would reach all somatosensory cortical areas within a relatively small time interval, and consequently, there would be no need to 'bind' this type of information together.

Methods

SURGICAL AND ELECTROPHYSIOLOGICAL PROCEDURES. In each animal, multiple microelectrode arrays (NBLABS, Dennison, Texas), each containing 16 teflon-coated, stainless steel microwires (50 µm in diameter) forming a 2 X 8 matrix (total sampling area, 2 mm^2), were chronically implanted in different cortical areas under general anesthesia (15 mg/kg ketamine, 5mg/kg xylazine and 1% halothane). During the surgical procedure for microwire array implantation, the receptive fields of single and multiple units were characterized to ensure correct placement of each array. Five to seven days after the surgical procedure, animals were seated in a recording chamber. A 96 channel many neuron acquisition processor (MNAP, Plexon, Dallas, Texas) was used to acquire and discriminate single neural unit activity from each of the implanted microwires. Time-amplitude discriminators and a modified version[18] of a principal component algorithm[32] were used to isolate single cortical units in real time. Analog samples of the waveforms of cortical potentials and the time of occurrence of each spike were stored. Off-line analyses of interspike interval histograms, autocorrelograms and waveform shapes were used to crossvalidate the on-line discrimination of single units. Once single units had been discriminated, punctate tactile stimulation (step pulses with 100 ms duration delivered at 1Hz) were delivered to different locations of the hand, forearm and face, using a computer-controlled vibromechanical probe driven by a Grass S8800 stimulator. A total of 360 trials were delivered at each skin site in a random sequence. Up to 25 skin sites were stimulated in each animal. Tactile stimulation was delivered in both awake and lightly anesthetized (ketamine i.m.) animals. The results obtained were virtually identical in both conditions.

SINGLE-TRIAL ANALYSIS OF NEURAL ENSEMBLE DATA. Three pattern-recognition techniques were used to measure the ability of neural ensembles located in three somatosensory cortical areas (3b, SII and area 2) to encode stimulus location on a single trial: linear discriminant analysis (LDA), a learning vector quantization (LVQ) artificial neural network (ANN), and a back-propagation (BP) ANN. Our procedures for applying LDA, a classical multivariate statistical technique, have been described[33]. The BP ANN was chosen because it is widely used for non-linear pattern recognition, not only in computer science and engineering[34] but also in neuroscience, where it has been used in a variety of studies[5,35,36]. The LVQ ANN was chosen because it provides a nonparametric technique for classifying large and sparse non-linear pattern vectors[37]. This made the LVQ ANN an attractive option for single-trial classification of input patterns from simultaneous multi-neuron recordings. A multiprocessor pentium-based workstation running MATLAB (Mathworks, Boston, Massachusetts) and its statistics and neural network toolboxes was used for all pattern recognition analysis. We used a modified LVQ ANN to apply the Kohonen's optimized-learning-vector quantization algorithm, which is a supervised version of Kohonen's self-organizing feature map[37]. The network included two hidden units and one output unit per class (i.e. stimulus site) to be discriminated. Thus, when data from three locations were used, the networks had 6 hidden units and 3 output units. The number of training epochs used in these analyses were the product of the number of hidden units and the number of training trials. The feedforward BP ANN was configured as a supervised learning technique that produced parametric outputs in probabilistic ranges. It used two hyperbolic tangent hidden units per class (skin site) and one log sigmoid output unit per class, and trained using the resilient BP learning rule. The number of training epochs used was determined by 'early stopping'[38], with increments of 100 epochs.

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1. Kaas, J. H. & Pons, T. P. in *Comparative Primate Biology* 4, 421–468 (ed. Steklis, H.D. & Erwin,. J) (Alan R. Liss, New York, 1988).
2. Hopfield, J. J. Pattern recognition computation using action potential timing for stimulus representation. *Nature* 376, 33–36 (1995).
3. Hopfield, J. J. & Herz, A. V. Rapid local synchronization of action potentials: toward computation with coupled integrate-and-fire neurons. *Proc. Natl. Acad. Sci., USA* 92, 6655–6662 (1995).
4. Grossberg, S. How does a brain build a cognitive code? *Psychol. Rev.* 87, 1–51 (1980).
5. Middlebrooks, J. C., Clock, A. E., Xu, L. & Green, D. M. A panoramic code for sound location by cortical neurons. *Science* 264, 842–844 (1994).
6. Hebb, D. O. *The Organisation of Behavior* (Wiley, New York, 1949).
7. Erickson, R. P. Stimulus encoding in topographic and non-topographic afferent modalities: on the significance of the activity of individual sensory neurons. *Psychol. Rev.* 75, 447–465 (1968).
8. Wise, S. P. & Desimone, R. Behavioral neurophysiology: insights into seeing and grasping. *Science* 242, 736–741 (1988).
9. Bullier, J. & Nowak, L. G. Parallel versus serial processing: new vistas on the distributed organization of the visual system. *Curr. Opin. Neurobiol.* 5, 497–503 (1995).
10. Schiller, P. H. On the specificity of neurons and visual areas. *Behav. Brain Res.* 76, 21–35 (1996).
11. Georgopoulos, A. P., Schwartz, A. B. & Kettner, R. E. Neuronal population encoding of movement direction. *Science* 233, 1416–1419 (1986).
12. Churchland, P. S. & Sejnowski, T. J. *The Computational Brain* (MIT Press, Cambridge, Massachusetts, 1992).
13. Nicolelis, M. A. L., Ghazanfar, A. A., Faggin, B. M., Votaw, S. & Oliveira, L. M. O. Reconstructing the engram: simultaneous, multisite, many single neuron recordings. *Neuron* 18, 529–537 (1997).
14. Nicolelis, M. A. L., Stambaugh, C. R., Brisben, A. & Laubach, M. in *Methods in Neural Ensemble Recordings* (ed. Nicolelis, M. A. L.) (CRC, New York, in press).
15. Kaas, J. H. in *Aotus: the Owl Monkey* (eds Baer, J. F., Weller, R. E. & Kakoma, I.) 322–347 (Academic, San Diego, 1994).
16. Chapman, C. E. & Ageranioti-Belanger, S. A. Discharge properties of neurones in the hand area of primary somatosensory cortex in monkeys in relation to the performance of an active tactile discrimination task. I. areas 3b and 1. *Exp. Brain Res.* 87, 319–339 (1991).

17. Iwamura, Y., Tanaka, M. & Hikosaka, O. Overlapping representations of fingers in the somatosensory cortex (area 2) of the conscious monkey. *Brain Res.* 197, 516–520 (1980).
18. Nicolelis, M. A. L. & Chapin, J. K. Spatiotemporal structure of somatosensory responses of many-neuron ensembles in the rat ventral posterior medial nucleus of the thalamus. *J. Neurosci.* 14, 3511–3532 (1994).
19. Nicolelis, M. A. L., Baccala, L. A., Lin, R. C. & Chapin, J. K. Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system. *Science* 268, 1353–1358 (1995).
20. Bell, A. J. & Sejnowski, T. J. An information maximization approach to blind separation and blind deconvolution. *Neural Comput.* 7, 1129–1159 (1995).
21. Vaadia, E. *et al.* Dynamics of neuronal interactions in monkey cortex in relation to behavioral events. *Nature* 373, 515–518 (1995).
22. Seidemann, E., Meilijson, I., Abeles, M., Bergman, H. & Vaadia, E. Simultaneously recorded single units in the frontal cortex go through sequences of discrete and stable states in monkeys performing a delayed localization task. *J. Neurosci.* 16, 752–768 (1996).
23. Singer, W. & Gray, C. M. Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* 18, 555–586 (1995).
24. Shadlen, M. N. & Newsome, W. T. Noise, neural codes and cortical organization. *Curr. Opin. Neurobiol.* 4, 569–579 (1994).
25. Ferrington, D. G. & Rowe, M. Differential contributions to the coding of cutaneous vibratory information by cortical somatosensory areas I and II. *J. Neurophysiol.* 43, 310–331 (1980).
26. Merzenich, M. M. & Kaas, J. H. Principles of organization of sensory-perceptual systems in mammals. *Prog. Psychobiol. Physiol. Psych.* 9, 1–41 (1980).
27. Kaas, J. H. & Garraghty, P. E. Hierarchical, parallel, serial arrangements of sensory cortical areas: connection patterns and functional aspects. *Curr. Opin. Neurobiol.* 1, 248–251 (1991).
28. Van Essen, D. C., Anderson, C. H. & Felleman, D. J. Information processing in the primate visual system: an integrated systems perspective. *Science* 255, 419–423 (1992).
29. Nicolelis, M. A. L., Fanselow, E. E. & Ghazanfar, A. A. Hebb's dream: the resurgence of cell assemblies. *Neuron* 19, 219–221 (1997).
30. McClurkin, J. W. & Optican, L. M. Primate striate and prestriate cortical neurons during discrimination. I. simultaneous temporal encoding of information about color and pattern. *J. Neurophysiol.* 75, 481–495 (1996).
31. Victor, J. D. & Purpura, K. P. Nature and precision of temporal coding in visual cortex: a metric-space analysis. *J. Neurophysiol.* 76, 1310–1326 (1996).
32. Abeles, M. & Goldstein, M. Multiple spike train analysis. *IEEE Proc.* 65, 762–773 (1977).
33. Nicolelis, M. A. L., Lin, R. C. S. & Chapin, J. K. Neonatal whisker removal reduces the discrimination of tactile stimuli by thalamic ensembles in adult rats. *J. Neurophysiol.* 78, 1691–1706 (1997).
34. Bishop, C. M. *Neural Networks for Pattern Recognition* (Oxford Univ. Press, New York, 1995).
35. Zipser, D. & Andersen, R. A. A back-propagation programmed network that simulates response properties of a subset of posterior parietal neurons. *Nature* 331, 679–684 (1988).
36. Johnson, K. O., Hsiao, S. S. & Twombly, I. A. in *The Cognitive Neurosciences* (ed. Gazzaniga, M. S.) 253–267 (MIT Press, Cambridge, Massachusetts, 1997).
37. Kohonen, T. *Self-Organizing Maps* (Springer, New York, 1997).
38. Sarle, W. S. Stopped training and other remedies for overfitting. *Proc. 27th Symp. Interface Comp. Sci. Stat.* 1, 352–360 (1995).