SI Neuron Response Variability Is Stimulus Tuned and NMDA Receptor Dependent

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Whitsel, B. L., O. Favorov, K. A. Delemos, C.-J. Lee, M. Tommerdahl, G. K. Essick, and B. Nakhle. SI neuron response variability is stimulus tuned and NMDA receptor dependent. J. Neurophysiol. 81: 2988–3006, 1999. Skin brushing stimuli were used to evoke spike discharge activity in single skin mechanoreceptive afferents (sMRAs) and anterior parietal cortical (SI) neurons of anesthetized monkeys (Macaca fascicularis). In the initial experiments 10–50 presentations of each of 8 different stimulus velocities were delivered to the linear skin path from which maximal spike discharge activity could be evoked. Mean rate of spike firing evoked by each velocity (MFR) was computed for the time period during which spike discharge activity exceeded background, and an across-presentations estimate of mean firing rate (MFR) was generated for each velocity. The magnitude of the trial-by-trial variation in the response (estimated as CV; where CV = standard deviation in MFR/MFR) was determined for each unit at each velocity. MFR for both sMRAs and SI neurons (MFRsMRA and MFRsSI, respectively) increased monotonically with velocity over the range 1–100 cm/s. At all velocities the average estimate of intertrial response variation for SI neurons (CVsSI) was substantially larger than the corresponding average for sMRAs (CVsMRA). Whereas CVsMRA increased monotonically over the range 1–100 cm/s, CVsSI decreased progressively with velocity over the range 1–10 cm/s, and then increased with velocity over the range 10–100 cm/s. The position of the skin brushing stimulus in the receptive field (RF) was varied in the second series of experiments. It was found that the magnitude of CVsSI varied systematically with stimulus position in the RF: that is, CVsSI was lowest for a particular velocity and direction of stimulus motion when the skin brushing stimulus traversed the RF center, and CVsSI increased progressively as the distance between the stimulus path and the RF center increased. In the third series of experiments, either phencyclidine (PCP; 100–500 μg/kg) or ketamine (KET; 0.5–7.5 mg/kg) was administered intravenously (iv) to assess the effect of block of N-methyl-D-aspartate (NMDA) receptors on SI neuron intertrial response variation. The effects of PCP on both CVsSI and MFRsSI were transient, typically with full recovery occurring in 1–2 h after drug injection. The effects of KET on CVsSI and MFRsSI were similar to those of PCP, but were shorter in duration (15–30 min). PCP and KET administration consistently was accompanied by a reduction of CVsSI. The magnitude of the reduction of CVsSI by PCP or KET was associated with the magnitude of CVsSI before drug administration: that is, the larger the predrug CVsSI, the larger the reduction in CVsSI caused by PCP or KET. PCP and KET exerted variable effects on SI neuron mean firing rate that could differ greatly from one neuron to the next. The results are interpreted to indicate that SI neuron intertrial response variation is 1) stimulus tuned (intertrial response variation is lowest when the skin stimulus moves at 10 cm/s and traverses the neuron’s RF center) and 2) NMDA receptor dependent (intertrial response variation is least when NMDA receptor activity contributes minimally to the response, and increases as the contribution of NMDA receptors to the response increases).

INTRODUCTION

The magnitude of the anterior parietal cortical (SI) response to a mechanical skin stimulus undergoes prominent fluctuations from one stimulus presentation to the next. Trial-by-trial fluctuations of the SI response to the same stimulus (intertrial response variation) are obvious regardless of the recording method employed; that is, the SI neuron population response recorded with a large surface electrode, the action potential train of a single SI neuron recorded with a microelectrode from an extracellular location, and the change in transmembrane potential change recorded intracellularly from a neuron’s dendrite or soma all exhibit substantial trial-by-trial variability despite extensive precautions to ensure constancy of stimulus and experimental conditions. A large trial-by-trial variability is not unique to the stimulus-evoked response of SI cortex or of individual SI neurons. For example, prominent trial-by-trial variation of the response of both single neurons and neuron populations of other primary sensory cortical regions has been described (for recent descriptions of the large variability in the visual cortical response see Arieli et al. 1996; Azouz and Gray 1999; deRuyter et al. 1997; Ferster 1996; Shadlen and Newsome 1994, 1995, 1998; for divergent view see Gur et al. 1997).

The fact that the trial-by-trial fluctuations in the mean firing rate response of a single SI neuron to a repeated, identical mechanical skin stimulus typically are 10–30 times larger than the variations in the response of a single mechanoreceptive afferent fiber (sMRA) studied in the same way (Essick and Edin 1995; Lee and Whitsel 1992; Whitsel et al. 1993, 1977; Young et al. 1978) suggests that CNS mechanisms account for the largest fraction of the response variation observed at the level of SI cortex. Unfortunately, little or no detailed information is available concerning the mechanisms that, on a trial-by-trial basis, could modify the efficacy of transmission of stimulus-evoked neuroelectrical activity over the projection pathways that link sMRAs and SI neurons. The dearth of information about the CNS mechanisms responsible for the large variability of the SI response to repetitive sensory stimulus was the major impetus for this study.

Previous studies of information processing by SI cortex have assumed that 1) randomness in the processes that underlie...
synaptic transmission at each level of the sMRA-to-SI projection path, and in the processes that generate the spike train responses of individual sMRAs underlies the prominent trial-by-trial fluctuations in both the SI cortical responses and perceptual experiences evoked by sensory stimuli; 2) the magnitude of the trial-by-trial fluctuations in signal transmission over the sMRA-to-SI neuron projection path does not change systematically or substantially with changing stimulus conditions; and 3) the sources that contribute to sMRA and CNS somatosensory neuron response variation act collectively to impose a fixed upper limit on the capacity of SI cortex to detect and respond differentially to somatic stimuli. To the contrary, the observations obtained in this study suggest that the CNS mechanisms that determine SI neuron response variation are not invariant, but operate dynamically to minimize response variation over the same range of conditions of skin brushing stimulation optimal for human tactile motion perceptual discrimination (Essick 1997; Essick and Whitsel 1985a; Whitsel et al. 1972).

Some of the findings were communicated previously (Prince et al. 1994; Whitsel et al. 1993).

METHODS

Skin brushing stimuli

A computer-controlled DC torque motor (Cantek) was used to deliver skin brushing stimuli. The skin path contacted by the brush was defined by a rectangular opening in an aperture plate in stationary contact with the skin. This stimulator permits the delivery of brushing stimuli at velocities between 0.1 and 250 cm/s with a high degree of accuracy (±1% for velocities between 1 and 100 cm/s). Software allows a number of parameters of brushing stimulation to be specified from a computer keyboard: velocity, direction, interstimulus interval (ISI), and number of stimulus presentations in a “run.” Other stimulus parameters (orientation, location within the RF, traverse length, traverse width, force) are determined by adjusting the position of the stimulator (orientation and location within the RF), by using an aperture plate with an opening with the desired dimensions (traverse length and width), and by using a brush with the desired stiffness (force). In the experiments of this study, these “other” parameters of skin brushing stimulation were adjusted to optimize the response of each SI neuron and sMRA studied. The range of traverse lengths used was 2.0–8.5 cm; traverse width was either 0.5 or 1.0 cm. No stimulus exerted a force on the skin >10 g.

Neurophysiological recording

SI NEURON RECORDING. Macaca fascicularis monkeys of either sex were studied. Under deep general anesthesia (1–4% halothane in oxygen) and after intramuscular injection of a glucocorticoid (Solu-Medrol, 5–10 mg), a 2-cm diameter circular opening was made in the skull overlying SI cortex and a recording chamber installed over the opening with dental acrylic. A catheter was inserted in a hindlimb vein to allow intravenous (iv) administration of drugs and maintenance solutions (0.9% NaCl and 5% dextrose). All surgical sites were infiltrated and topically dressed with long-acting local anesthetic and closed with sutures. After the surgical procedures had been completed, neuromuscular block was achieved by administration of vecuronium bromide (Norcuron, 0.1 mg/kg iv loading dose, 1 μg·kg⁻¹·min⁻¹ thereafter), positive pressure ventilation was provided, and end-tidal CO₂ was maintained between 3.0 and 4.5% by adjustments of respirator rate and volume.

After neuromuscular block and initiation of ventilation with a halothane (0.5–1.0%), nitrous oxide (50–67%), and oxygen (≥20%) anesthetic gas mixture, a 2- to 3-h “rest period” was allowed for stabilization of electroencephalogram (EEG) and autonomic parameters. The halothane/nitrous oxide/oxygen gas mixture used in the cortical recording experiments exerts minimal effects on somatosensory cortical neuron response and receptive field (RF) properties (Duncan et al. 1982), but eliminates or greatly attenuates both the alterations of electrocortical slow-wave activity (EEG desynchronization) and cardiovascular/autonomic reactions (e.g., elevations in heart rate and blood pressure) characteristic of conscious subjects exposed to unanticipated nonnoxious tactile stimuli. The EEG was monitored by low-pass filtering (0.1–100 Hz) the signal recorded by the intracortical microelectrode, and also by a Ag-AgCl electrode in contact with either the dura or cortical surface at the periphery of the region studied with microelectrode penetrations. The electrocardiogram was recorded using a three-lead system of skin electrodes. Microelectrode recordings of SI neuron activity were obtained either transdurally or through an opening in the dura overlying the region of interest. Throughout each recording session, the recording chamber was filled with artificial cerebrospinal fluid and sealed with a glass plate containing an “o”-ring that allowed microelectrode penetrations to be performed under “closed-chamber” conditions.

SI neuron spike discharge activity was recorded extracellularly using glass-insulated tungsten microelectrodes (impedance 200–500 kΩ at 10 kHz). Amplifier band-pass for recording of single neuron discharge was 0.6–6 kHz. Action potentials from single neurons were identified on the basis of both amplitude and waveform. Digital records of the times of occurrence of action potentials and stimulus events were created on-line, and the neural and stimulus events also were stored as analog records (on videotape using a VCR and multichannel interface).

The apparatus and general approach used for extracellular single SI neuron recording were designed to minimize sensory input other than that evoked by application of skin brushing stimulus to the RF of each neuron studied. To this end, neither the supporting frame nor the recording apparatus made direct contact with the subject; the body was supported by contoured padding, and the sensory consequences of the surgical procedures were minimized by reconstructing the surgical fields (with sutures) and dressing all wound margins with long-acting local anesthetic. The apparatus allowed rapid changes in the composition of the anesthetic gas mixture (whenever dictated by EEG and autonomic signs) and replacement of the recording electrode in the absence of direct contact with either the recording chamber or the subject.

sMRA RECORDING. Records of the spike trains evoked in large-diameter sMRAs by skin brushing stimuli were available as part of a database of single and multineuron recordings obtained in previous experiments. This database was the source of all the sMRA data to be presented in this paper. Because the methods used to record stimulus-evoked spike discharge from individual sMRAs were described previously (Lee and Whitsel 1992; Whitsel et al. 1972; Young et al. 1978), they will be described only briefly.

In the sMRA recording experiments, deep surgical anesthesia was produced and maintained using pentobarbital sodium (PB; initial dose 25–40 mg/kg iv; supplemented on a regular schedule, typically 5–10 mg · kg⁻¹ · h⁻¹), and neuromuscular block was achieved using gallamine triethiodide. Positive pressure ventilation was provided, and end-tidal CO₂ and rectal temperature were monitored and maintained at normal resting values (3.5–5.5%; 37.5°C). A cutaneous peripheral nerve was exposed by blunt dissection and bathed in a pool of warm sterile mineral oil. The nerve then was transected, and fine filaments were dissected from the distal part of the transected nerve trunk. Each filament was placed over a Ag-AgCl electrode connected to the headstage of the recording system, and the region of skin innervated by the sMRAs in the filament was determined by monitoring the multunit discharge activity evoked by mechanical skin stimuli applied with a fine probe and/or brush. Once the skin locus from which
multunit activity could be elicited reliably by gentle mechanical stimuli had been identified, the filament was subdivided repeatedly until the spike discharge activity evoked in the filament satisfied accepted criteria for single-unit (sMRA) recording; that is, uniformity of amplitude and waveform of action potentials, and consistency of the RF and response characteristics with those described as characteristic of sMRAs. All procedures for recording the stimulus-evoked discharge activity of both sMRAs and SI neurons were reviewed and approved in advance and are in full compliance with National Institutes of Health guidelines and policy on animal welfare.

**General procedures**

Subjects were killed by administration of PB (40 mg/kg iv), followed by intracardial infusion of 0.9% saline and, in turn, by 10% neutral buffered Formalin. After intracardial infusion, the cortical region traversed by microelectrode penetrations was removed, blocked, and postfixed before histological processing. Each cortical block was infiltrated with 30% sucrose and sectioned in the sagittal plane at 30 μm. Sections were stained with cresyl fast violet, mounted on glass slides, and coverslipped. The sections were scanned microscopically to identify 1) the tracks created by the recording microelectrodes and 2) the locations of electrolytic lesions created by passing DC current through the recording microelectrode. The cytoarchitectonic areas from which single-unit recording were obtained were identified using the criteria of Powell and Mountcastle (1959) for differentiation of areas 3b, 1, and 2, and Jones and Porter (1980) for identification of area 3a. All recordings were obtained from layers III–V of areas 3b and 1.

**Neural spike train data processing and analysis**

Raster plots of spike trains and peristimulus (PST) histogram plots were generated from the data obtained from each unit. The index of stimulus-evoked, single-trial response magnitude used for both SI neurons and sMRAs was the average frequency of neural spike discharge (overall mean firing rate, MFR) during the entire period over which the response exceeded the background level of spike discharge activity. For most sMRAs and SI neurons, and at most stimulus velocities, this period corresponded closely to the time during which the brush was in contact with the RF. At the highest stimulus velocities, however, it was not unusual for the stimulus-evoked response to continue for a time after the brushing stimulus had broken contact with the skin. When the times of initial and final brush contact with the skin did not match the period during which a unit’s response was elevated (never observed at velocities <50 cm/s), the response period was considered to start at the point at which discharge activity first exceeded background (background was defined as the average level of discharge activity present before stimulus delivery), and to continue until spike discharge activity first returned to background. Background firing rate (“spontaneous activity”) was not subtracted from the mean firing rate during stimulation.

Magnitude of intertrial variability of the stimulus-evoked response of an sMRA or SI neuron was estimated by the coefficient of variation in MFR (CV), computed as

\[
CV = \frac{SD_{MFR}}{MFR} \times 100
\]

(1)

SI neuron directional sensitivity was estimated using an index \( \Delta' e \) derived from sensory decision theory (Essick and Whitsel 1985a,b)

\[
\Delta' e = \frac{MFR_{direction 1} - MFR_{direction 2}}{0.5 \times (SD_{MFR direction 1} + SD_{MFR direction 2})}
\]

(2)

**Stimulus protocol and sample size**

The same protocol (the “standard protocol”) was used to obtain data from each sMRA \( n = 25 \) and SI neuron \( n = 25 \) studied in the initial series of experiments. This protocol delivered eight different velocities of brushing stimuli (1, 2.5, 5, 10, 25, 50, 75, and 100 cm/s) to the path in the RF from which the most vigorous spike discharge activity could be evoked (the optimal skin path). The other characteristics of the standard protocol were as follows: each of the two available (opposing) directions of motion was delivered at every velocity; 10–30 presentations of each velocity were applied in each direction; order of brushing stimulus presentation was randomized for velocity and direction of motion; and ISI was 3.5–5 s.

The 25 sMRAs studied included 13 slowly adapting (SA) afferents, 10 rapidly adapting (RA, hair) afferents, and 2 Pacinian (PC) afferents; all had an RF on hindlimb hairy skin. This representation of the different classes of sMRAs in the sample population does not differ substantially from the proportions of large-diameter cutaneous mechanoceptive afferent types found within nerves that innervate hairy skin in human subjects (Vallbo et al. 1995). To ensure that the standard protocol was completed in 45–60 min, each stimulus velocity <10 cm/s was presented 10 times, each velocity between 10 and 25 cm/s was repeated 25 times, and each velocity above 25 cm/s was delivered 50 times. The higher velocity stimuli were delivered a larger number of times to compensate for the progressive decrease in the reliability of estimates of unit response magnitude with increasing velocity of skin brushing stimulation; because the duration of a brushing stimulus decreases with increasing velocity, neuron response duration also decreases, and this, in turn, decreases the reliability of the measure of the stimulus-evoked response that is obtained on each stimulus trial. For technical reasons (e.g., early termination of the protocol due to loss of unit isolation, or to stimulator/controller malfunction) an incomplete set of observations was obtained from 11 of the 25 SI neurons and from 3 of the 25 sMRAs studied using the standard protocol.

A less time-consuming protocol (the “reduced protocol”) was used to study the effects on SI neurons 1) of place of brushing stimulation in the RF (9 neurons: the series 2 experiments), and 2) of centrally acting drugs (38 neurons: the series 3 experiments). The reduced protocol also was used to determine whether changes in SI neuron RF properties accompanied the trial-by-trial fluctuations in the mean firing rate response to repeated applications of the same brushing stimulus (10 neurons were studied to evaluate the relationship between intertrial response variation and RF properties; these neurons were among those studied in the 2nd and 3rd series of experiments).

**Drug dosage and route of administration**

It was anticipated that the doses of ketamine (KET; 0.5–7.5 mg/kg) and phencyclidine (PCP; 100–500 μg/kg) that were used would achieve CNS concentrations that would block ~50% of cortical N-methyl-d-aspartate (NMDA) receptors (for recent reviews of non-competitive NMDA receptor antagonists, see Iversen and Kemp 1994; Iversen et al. 1989; Lodge et al. 1994). This estimate of drug effectiveness is based on 1) the concentrations in the cerebrospinal fluid and the cortical extracellular compartment achieved at these doses, and 2) the ability of PCP and KET to antagonize \(^1\)H][MK-801 binding in the rat cortical slice (Wong et al. 1986). At these doses, PCP and KET do not cause either synchrony in cortical neuron “spontaneous” activity or regular oscillations in single neuron response to sensory drive; these outcomes are encountered routinely with higher doses and would prevent meaningful evaluation of intertrial response variation.

Approaches for localized drug delivery (microdialysis, pressure injections) were not employed because it was felt that such methods could not effectively or reliably eliminate NMDA receptor-mediated influences that unsubtletly I) arise at multiple sites in somatosensory cortex and 2) are conveyed to different compartments of the target neurons via multiple, indirect, and spatially distributed routes. A second reason for systemic (intravenous) administration of the drugs was that this approach, unlike the approaches for applying...
drugs directly to the neurons under study, permits an effective drug concentration to be maintained in the cortical network over the lengthy time period needed to characterize the response of an SI neuron to repetitive skin brushing after drug administration. However, one should be aware that intravenous administration has the considerable disadvantage that one cannot be certain of the site(s) of drug action responsible for any effect(s) the drug might have on SI neuron response.

RESULTS

Effects of stimulus velocity on sMRAS and SI neurons

The raster plots of Fig. 1 show spike trains recorded from an sMRA (top panel) and SI neuron (bottom panel) during the delivery of four velocities (5, 25, 50, and 100 cm/s) of a skin brushing stimulus that, on every trial, moved in the same direction across the same skin path. The first 10 responses of each unit to each velocity are illustrated. It should be evident that, for both units, each increase in stimulus velocity was accompanied by an increase in mean rate of spike firing (MFR), and by a decrease in the number of stimulus-evoked spikes. Similar effects of increasing velocity were obtained from all 25 sMRAs studied with the standard protocol, and from 25 of the 29 SI neurons studied in the same way.

For each sMRA and SI neuron studied with the standard protocol, the eight across-trial estimates of MFR obtained (1 estimate for each stimulus velocity) were plotted to yield a "velocity versus MFR plot" (Fig. 2). Twenty-two sMRAs were studied using opposite directions of motion; thus each of these 22 sMRAs yielded 2 velocity versus MFR plots (1 for each direction; accounting for 44 of the 47 superimposed plots in bottom left panel in Fig. 2). For three sMRAs, only the responses to brushing stimuli delivered in one direction of motion were obtained.

Figure 2, bottom left panel, reveals that the higher the velocity of brushing stimulation, the larger was the MFR of an

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**FIG. 1.** Spike trains of a skin mechanoreceptive afferent (sMRA) and anterior parietal cortical (SI) neuron. Ten responses of an sMRA (top) and SI neuron (bottom) to a same-direction skin brushing stimulus applied at 4 different velocities (5, 25, 50, and 100 cm/s). Times of initial and final brush contact indicated by arrows along x-axis. Values of mean firing rate (MFR) and coefficient of variation (CV) indicated at right of each plot. sMRA data were obtained from rapidly adapting (RA) hair follicle afferent; SI neuron spike train data were obtained from cell in layer III of area 3b.
sMRA. The effect of an increase in velocity on MFR was highly consistent: in 136 of the 143 instances in which the responses of the same sMRA to neighboring velocities were compared (in excess of 96% of the comparisons), the MFR elicited by the nearest higher velocity exceeded the MFR associated with the lower velocity. The plot in the bottom right panel of Fig. 2 shows the “pooled” (across unit) velocity versus MFR relationship generated from the sMRA data.

Velocity of skin brushing also influenced SI neuron mean firing rate in a way that was relatively consistent from one SI neuron to the next. The 39 velocity versus MFR plots obtained from SI neurons are shown in the top left panel of Fig. 2, and the pooled relationship generated from the data obtained from all 25 SI neurons is shown at the top right. Fourteen of the 25 SI neurons were studied using both (opposite) directions of motion applied to the same skin path (accounting for 28 of the 39 plots in the top left panel of Fig. 2); data from the remaining 11 neurons were obtained using only one direction of motion. In >98% of the instances in which the responses of the same neuron to neighboring stimulus velocities were compared (in 156 of 163 instances), the nearest higher-velocity stimulus was associated with a larger MFR.

Comparison of SI neuron and sMRA response variation

Although inspection of the spike train raster plots obtained from each unit (e.g., such as those in Fig. 1) strongly suggested that the magnitude of intertrial response variation of an SI neuron studied at a given velocity exceeded that of an sMRA studied at the same velocity, we sought to ascertain whether this impression could be confirmed objectively. To this end, the across-unit average CV in the response of both sMRAs and SI neurons (CV_{sMRA} and CV_{SI}, respectively) to each stimulus velocity was determined. The plots in Fig. 3 make it evident that at every velocity CV_{sMRA} is lower than CV_{SI}; and statis-

**FIG. 2.** Effects of stimulus velocity on SI neurons and sMRAs. Left: superimposed velocity vs. MFR plots for sMRAs (bottom) and SI neurons (top). Right: pooled velocity vs. response plots for sMRAs (bottom) and SI neurons (top). Flags indicate ±1 SE.

**FIG. 3.** Pooled estimates of intertrial response variation (CV). The CV vs. velocity relationship for sMRAs (●) is monotonic, whereas the relationship for SI neurons (○) has 2 distinct limbs: the limb from 1 to 10 cm/s has a negative slope, whereas the limb from 10 to 100 cm/s has a positive slope.
tendency for the error in estimating unit MFR to increase as stimulus velocity is increased. The functional importance of this observation is that it suggests a process located within the CNS. A non-CNS explanation for the negatively sloping initial limb of the CV versus velocity relationship for SI neurons appears very unlikely because CV_{sMRA} increases monotonically over the entire 1- to 100-cm/s range of stimulus velocities; this is the expected form of the relationship if the dominant contributor to response variation is the period of time over which the single trial estimates of MFR were obtained.

Although comparison of the pooled estimates of SI neuron and of sMRA trial-by-trial response variation (Figs. 3 and 4) was valuable because it demonstrated that the velocity dependency of the two type of units is different, combination of the data obtained from different units obscures an impressive, and potentially functionally important heterogeneity of the observations collected from individual SI neurons. This heterogeneity is made apparent by the differences between the velocity versus CV plots (each plot shows the data obtained from a different SI neuron) illustrated in Fig. 5. For example, for some SI neurons the magnitude of CV approximated the low variability characteristic of sMRAs over a relatively wide band of velocities (typically, between 1 and 25 cm/s; see right panels in Fig. 5). In contrast, for other SI neurons (left panels in Fig. 5) the magnitude of CV equaled or approached that of sMRAs only over a very narrow band of velocities. In fact, for some SI neurons of the latter type, the magnitude of CV approached that characteristic of sMRAs at only a single velocity. In striking contrast to the considerable neuron-to-neuron diversity in the velocity dependency of SI neuron response variation, the form of the velocity versus CV relationship for sMRAs studied using the same stimulus conditions was highly stereotyped: i.e., for all sMRAs studied in this way CV increased monotonically and relatively gradually over the velocity range 1–100 cm/s.

To what extent is SI neuron response variation influenced by direction of motion and stimulus position within the RF?

The finding that the responses of SI neurons to stimulus velocities in the vicinity of 10 cm/s exhibited sMRA-like (low) trial-by-trial response variation led us to ask whether other parameters of skin brushing stimulation (e.g., direction of motion or position in the RF) might also influence the magnitude of SI neuron response variation.

DIRECTION OF STIMULUS MOTION. The data shown in Fig. 6 were obtained from four different SI neurons studied by applying opposing directions of motion to the optimal path in the RF. It should be noted that for each of these neurons the magnitude of the difference in the MFR responses to opposing directions of motion applied at the same velocity is different (the difference in the responses to opposing directions of same-velocity stimulus motion is least for the SI neuron that provided the data in the bottom right panel of Fig. 6, is greatest for the neuron that provided the data in the top left panel, and is intermediate for the 2 neurons whose data are shown in the top right and bottom left panels). Although inspection of data in Fig. 6 reveals that there is a tendency for the CV associated with a given velocity to be lowest for the direction of motion that led to the highest mean firing rate response at that same velocity (this is particularly evident in the data for the directional selective neurons at the top left, top right, and bottom left panels).
of Fig. 6), it also is evident that the extent to which a neuron responded differentially to stimulus direction did not cause fundamental modification of the way in which velocity influenced the magnitude of intertrial response variation. That is, the general form of the velocity-CV relationship of each neuron shown in Fig. 6 remains the same when the response is evoked by opposite directions of stimulus motion across the RF, even in those instances when the opposing directions evoked very different MFRs. Moreover, it should be noted that the tendency for CV to be lower for the direction of motion that led to the highest mean firing rate was least evident at velocities in the vicinity of 10 cm/s; that is, for most neurons minimal or near-minimal CV values were obtained at velocities in the vicinity of 10 cm/s, regardless of the direction of motion applied to the optimal skin path. Results similar to those shown in Fig. 6 were obtained for all SI neurons studied with the complete standard protocol (n = 14; 6 were directionally selective).

Position of the stimulus in the RF. The influence of position of the brushing stimulus in the RF was investigated by delivering a repetitive stimulus to the optimal path in the RF, and also to one or more linear paths that paralleled, but did not overlap the optimal path. A different protocol (the reduced protocol) was used in such experiments to minimize the time required to estimate the magnitude of the response variation associated with the neuron’s response to stimulation at each RF position. Specifically, the reduced protocol applied 10–25 presentations at a single, preselected velocity of brushing motion (usually between 5 and 25 cm/s) to each path in the RF in each of the opposing directions of motion; ISI was 3.5–5 s. Use of this protocol yielded an estimate of CV for each combination of stimulus path and direction of motion studied. Information about the effects of stimulus position in the RF on CV was obtained from nine SI neurons.

Results obtained from an SI neuron studied by applying the stimulus at different positions in the RF are shown in Fig. 7. The RF of this neuron was on the hairy skin of the lateral, posterior, and medial surfaces of the contralateral calf, with the optimal skin path (the region yielding the highest mean rate firing response) occupying a central position on the medial calf (M. Cen.). A total of five nonoverlapping parallel linear paths (indicated by arrows on the figurine at the top left of Fig. 7) were studied. Twenty-five presentations of each of the opposing directions of motion were delivered to each path; stimulus velocity was always 12.5 cm/s.

The panels at the bottom of Fig. 7 reveal that the magnitude of
the trial-by-trial fluctuations in the response of this SI neuron to the preferred direction of motion (proximal-to-distal; P→D) changed in an orderly way when the stimulus was moved to different positions in the RF; the fluctuations of the response to P→D motion in the RF were smallest at the M. Cen. skin path (bottom left panel), were somewhat larger at M. Ant. (bottom middle panel), and were largest at the L. Ant. path (bottom right panel). The more complete presentation of the data obtained from the same neuron (the plots at the top right of Fig. 7 summarize the observations obtained in both directions of motion) shows that CV was 1) smallest when delivery of opposing directions of motion to the skin led to very different MFRs (this is especially evident at path M. Cen) and 2) greatest when the difference between the MFRs evoked by the opposing directions of motion were least (this is most evident at the RF path designated as L. Ant.). Similar results were obtained from all five of the directionally selective SI neurons studied in this way.

For the adirectional SI neurons (n = 4) studied in the same way as the neuron shown in Fig. 7, the magnitude of CV also varied systematically when the path taken by the stimulus was shifted within the RF; that is, the larger the distance between the skin path actually stimulated and the optimal skin path, the higher was CV. These observations demonstrate that place-dependent variations in the magnitude of CV also influence the capacity of adirectional SI neurons to signal a stimulus that moves across the RF.

**Meaning of SI neuron response fluctuations**

We next sought to evaluate the possibility that trial-by-trial changes in the magnitude of the response of an SI neuron to the same brushing stimulus might reflect trial-by-trial changes in the distribution of sensitivity within the skin region contacted by the stimulus. The approach used to investigate this possi-
bility is illustrated in Fig. 8. Figure 8A shows the MFR response of an SI neuron to each presentation of a brushing stimulus (49 stimuli were delivered) that moved at 20 cm/s from proximal-to-distal across the dorsal hairy skin of digits 3 and 4 of the contralateral hindlimb. The scatter of the points along the y-axis in the plot in Fig. 8A indicates the prominent trial-by-trial fluctuations in the MFR response of this neuron (the MFR on this neuron fluctuated between 7 and 70 spikes/s).

The approach used to ascertain whether, and to what extent, the response fluctuations of the neuron illustrated in Fig. 8 corresponded to changes in the distribution of sensitivity within the RF consisted of the three following steps: 1) the

![Diagram](image.png)

**FIG. 7.** Effects of stimulus position on SI neuron CV. Plot at top right compares the values of MFR and CV (right ordinate) obtained at each of 5 different paths within the RF with the magnitude of directional sensitivity ($\Delta e'$) at each path. For this neuron CV was largest at skin path L. Ant. (CV = 32.1; plot at bottom right), least at path M. Cen. (CV = 9.2; plot at bottom left), and intermediate at path M. Ant. (CV = 24.9; plot at bottom middle). Note the systematic relationship between magnitude of CV and directional discriminative capacity: that is, where $\Delta e'$ is highest CV is lowest, and vice versa. Plots at bottom show trial-by-trial variations in MFR at 3 of the 5 stimulus paths within the RF.

![Diagram](image.png)

**FIG. 8.** Trial-by-trial variations in SI neuron response are accompanied by changes in the distribution of sensitivity on the skin (i.e., in RF size). A: trial-by-trial fluctuations in MFR; skin region stimulated and direction of motion indicated by arrow on figure; velocity was 20 cm/s; ISI was 3.5 s). B: partition of the MFR responses into 3 groups (I–III) based on magnitude (I $>$ II $>$ III). C and D: superimposed peristimulus time histograms (binwidth, 0.4 cm) computed from the responses belonging to groups I (C) and II (D); and to groups I (C) and III (D). E and F: ratio plots showing that response to RF center stimulation (+) remained relatively undiminished (indicated by ratio values near to 1.0) even on those trials (the trials assigned to either groups II or III) when the neuron’s response fell below the criterion for assignment to group I. This outcome indicates that losses of response magnitude at skin regions outside the RF center account for the major fraction of the decrease in the MFR response in the trials included in groups II and III.
individual responses were partitioned into three nonoverlapping groups based on magnitude (see plots at top right; group I includes the largest responses, group III the smallest responses, and the group II responses are intermediate), 2) a PST histogram (binwidth in cm) was generated for the trials in each response group, and the histograms for the different response groups were superimposed to facilitate their comparison (the histogram for the group II responses is superimposed on the histogram for the group I responses in C; D superimposes the histograms for the group III and group I responses), and 3) a ratio plot (Duncan et al. 1982; Lee and Whitel 1992) was computed for each pair of PST histograms (see Fig. 8, E and F; a value <1.0 in a ratio plot indicates that at this skin site the unit's sensitivity to the brushing stimulus was less than it was when the unit's response magnitude fell within group I, the highest response group; and conversely, a value >1.0 indicates that at this site the unit's sensitivity was greater than it was when the unit’s response fell within group I).

Inspection of the superimposed histograms (shown in the middle) and ratio plots (shown at the bottom) of Fig. 8 reveals that the fluctuations in SI neuron response magnitude were accompanied by substantial and regionally selective changes in the distribution of sensitivity within the RF. That is, when the response of the neuron to the skin brushing stimulus did not attain that of group I, it was not due to a uniform loss of sensitivity at all points within the stimulated skin path, but instead, to a selective loss of sensitivity at skin points outside the RF center (the RF center—the skin area exhibiting the maximal response to the brushing stimulus—is designated by the asterisks located above the PST histograms and ratio plots of Fig. 8). It also should be noted that the sensitivity of the RF center of the neuron remained essentially undiminished even during those trials when response magnitude was lowest. Similar findings were obtained from all SI neurons evaluated using the same approach (n = 10).

**CNS mechanism(s) involving NMDA receptors contribute to SI neuron ITV**

The reduced protocol also was used to study the effects on SI neuron trial-by-trial response variation of drugs known to selectively interact with one or another of the multiple classes of receptors that mediate the excitatory actions of synaptically released glutamate. All SI neurons studied for the purpose of evaluating the effects of drug administration (a total of 38 SI neurons) used either of two versions of the reduced protocol: 1) a single velocity of skin brushing stimulation was delivered in both of the available directions of motion (opposing) to the optimal skin path, or 2) a limited number of stimulus velocities (2–4) were applied in opposing directions to the optimal path.

Twenty-six SI neurons were studied both before and at multiple times after intravenous administration of 100–500 μg/kg of PCP (a selective noncompetitive antagonist of NMDA receptors) (Iversen et al. 1989; Lodge et al. 1989). Another 12 neurons were studied before and at multiple times after intravenous injection of 0.5–7.5 mg/kg of KET (another selective noncompetitive antagonist of NMDA receptors). Finally, 12 neurons were studied both before and after intravenous administration of 7–15 mg/kg PB (a barbiturate anesthetic that exerts actions via different mechanisms other than NMDA receptor antagonism, including potentiation of the actions of GABA at GABA<sub>A</sub> receptors). Whenever possible, a neuron was studied repeatedly (at selected time points after PCP or KET administration; usually no less frequently than once every 10 min) until response magnitude and intertrial variability had recovered to the levels observed before drug administration (typically 1–1.5 h for PCP, and 20–30 min for KET; no unit was studied long enough for recovery from PB). For each neuron studied in this way an estimate of across-trial mean firing rate (MFR) and intertrial variability (CV) was obtained at each time point by repetition of the exactly the same protocol.

Two representative examples of “raw” spike train data that show clear effects of intravenous PCP on the SI neuron trial-by-trial response variation associated with repetitive brushing of the optimal path in the RF are provided in Figs. 9 and 10. Note that, although the effect of PCP on the CV of both neurons is the same (the CV of both neurons is decreased after PCP), the effect on MFR is very different from one neuron to the next. Summarized briefly, for the SI neuron in Fig. 9, CV decreased and MFR increased following PCP; whereas for the neuron in Fig. 10 both CV and MFR decreased after PCP administration.

Data completely consistent with those shown in Figs. 9 and 10 were obtained from three SI neurons (each studied in different subject; using the reduced protocol) in which PCP was not applied systemically, but was applied topically to the cortical surface (in these experiments a concentration of 5 × 10<sup>-6</sup> M in the cerebrospinal fluid that bathed the cortical surface was achieved by microinjection of PCP into the recording chamber). In all three neurons studied in this way, topical PCP application reduced the trial-by-trial variation in the response to repetitive skin brushing and increased MFR. Similar effects of PCP on the SI neuron response variation associated with a quite different mode of skin stimulation (sinusoidal vertical skin displacement) also were obtained and will be reported in a subsequent paper. The results obtained using topical PCP application are viewed as consistent with the idea that the alterations of SI neuron CV and observed after intravenous administration of PCP or KET are mainly attributable to actions on somatosensory cortex, although the possibility that drug actions at subcortical sites contributed to those alterations cannot be ruled out.

The data obtained from the 38 SI neurons studied with intravenous PCP and/or KET were used to construct the plots shown in the top left and top middle panels of Fig. 11. These plots show the relationship between magnitude of CV associated with the predrug response to the repetitive brushing stimulus (CV<sub>pre</sub> on the x-axis) and the difference (on the y-axis) between the pre- (CV<sub>pre</sub>) and postdrug (CV<sub>post</sub>) CV values obtained at the time the drug effect was maximal (30–60 min after injection for PCP; 5–10 min after injection for KET). Statistical evaluation (using linear regression analysis; see Fig. 11 legend) of the data points in the top left and middle panels of Fig. 11 revealed that 1) the magnitude of the reduction in SI neuron CV that followed either PCP or KET (estimated by CV<sub>post</sub> – CV<sub>pre</sub>) is highly associated (P < 0.001) with the magnitude of CV measured before drug administration (that is, the higher the value of CV<sub>pre</sub> the larger the reduction in CV that accompanied NMDA receptor blockade by PCP or KET); and 2) the effect of PCP or KET on SI neuron CV was independent (P > 0.5) of the effect on (Fig. 11, left and middle panels at bottom).
In contrast, the effects of intravenous administration of PB on SI neuron CV (top right panel in Fig. 11; determined for another 12 SI neurons) and MFR (bottom right panel in Fig. 11) differ fundamentally from those of PCP or KET (compare panels in right column with left and middle columns of Fig. 11), whereas PCP and KET consistently decreased CV whenever SI neuron CV was high before drug administration, and had variable effects on MFR that were independent of the effect on CV, PB administration consistently increased CV and decreased MFR. The maximal effects of PB occurred within 5–20 min of the injection and, contrary to those of PCP and KET, remained evident until data collection was terminated (in some cases as long as 2–3 h after injection).

The high degree of similarity between the effects of PCP and KET on CV and MFR, and the striking differences between the effects of PB and those of PCP and KET evident in Fig. 11 are viewed as consistent with the idea that PCP and KET influence a common CNS mechanism (NMDA receptors), whereas PB acts via other, entirely different mechanisms. Linear regression analysis revealed that the magnitude of intertrial response variation obtained before drug administration (CV$_{PRE}$) and the difference in mean firing rates obtained before and after PCP or KET administration (MFR$_{PRE}$ - MFR$_{POST}$) were unrelated (Fig. 12).

### SI neuron discriminative capacity and intertrial response variability

It is infrequently acknowledged that for many SI neurons directional discriminative capacity is greatest at stimulus conditions that do not elicit maximal mean firing rates (Essick and Whitsel 1985a,b). An example of such a neuron is shown in Fig. 13. This SI neuron’s response to opposing directions of skin brushing stimulation to a path on the contralateral forearm skin was recorded at five different velocities of motion (1, 2.5, 5, 10, and 25 cm/s). Figure 13A, top plot (solid line), reveals that, although the across-trial mean firing rate (MFR) versus velocity plots (dotted lines) for the P → D and D → P stimuli diverge progressively with increasing velocity, this neuron’s capacity to discriminate between the opposing directions of motion (as estimated by $\Delta'e$) does not increase progressively as velocity is increased; that is, $\Delta'e$ is maximal at 5 cm/s and declines at both lower and higher velocities. The plots in Fig. 13B demonstrate the high negative correlation between the
Before drug administration the SI neuron that yielded the data shown in Fig. 14 signaled direction of motion most unambiguously at 15 cm/s (C, O), but less unambiguously at the lower velocities and also at the highest velocity, due to the higher levels of response variation associated with those velocities (CV, ●). Comparison of Fig. 14, B and D (the postdrug observations) with A and C (the predrug observations) reveals that, for this SI neuron, PCP administration led to a substantial modification of the velocity dependency of both CV and Δ'v. It also is evident that after PCP the optimal velocity (the velocity at which directional sensitivity was maximal) shifted to the highest velocity used (24 cm/s); an outcome attributable principally to the reduction of the intertrial response variation that followed PCP administration, because at both 15 and 24 cm/s the difference in the magnitude of the postdrug MFRs evoked by opposing directions of motion is less than it was before drug administration.

The effects of PCP-induced NMDA receptor block on yet another directionally selective SI neuron are shown in Fig. 15. In contrast to the neuron illustrated in Fig. 14, this neuron’s mean firing rate was increased after PCP administration (300 μg/kg iv; the MFRs observed before PCP administration and at a series of postinjection times are shown in Fig. 15, A and B). As was the case with the neuron shown in Fig. 14, however, PCP again caused 1) a prominent decrease in intertrial response variation (flags in Fig. 15, A and B, indicate ±1 SD in mean firing rate) and 2) substantially increased the neuron’s capacity to differentially signal both direction of motion in the RF (direction Δ'v, Fig. 15D) and velocity (velocity Δ'v, Fig. 15C) of brushing stimulation. The MFR data in Fig. 15A show that the postdrug increase in this neuron’s capacity to signal direction of motion at velocity 5.6 cm/s occurred in spite of a drug-induced reduction in the difference in the MFRs evoked by two directions of motion. Once again, therefore, the change in SI neuron discriminative capacity (increase in Δ'v) after NMDA receptor block is attributable to the drug-induced decrease in intertrial response variation, not to the alterations in mean firing rate.

**DISCUSSION**

**Comparison of response variation of sMRAs and SI neurons**

The initial series of experiments demonstrated that SI neurons exhibit larger trial-by-trial response variation than do sMRAs at each velocity of skin brushing stimulation studied (Fig. 3). This result is fully consistent with the idea that the magnitude of the trial-by-trial variations in sensory neuron response increases progressively with the number of synapses in the projection from sensory receptor to primary sensory cortex (Levine 1994; Petrovaara et al. 1986; Tolhurst et al. 1983). There is no precedent, however, for the finding that the dependency of the magnitude of SI neuron and sMRA response variation on velocity of skin brushing stimulation is very different (Fig. 3); CVs increases monotonically over the entire 1–100 cm/s velocity range, but CVs declines over the range 10–100 cm/s. Similarly, the observation that for some SI neurons CV is minimal over a relatively wide range of velocities, whereas for other SI neurons CV is minimal only over a very narrow range of velocities (Fig. 5) was not anticipated.

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**Effects of NMDA receptor block on SI neuron discriminative capacity**

Figure 14 shows the effects of NMDA receptor block produced by PCP (500 μg/kg iv) on a directionally selective SI neuron studied in the same way as the neuron shown in Fig. 13. Figure 13, A and B, shows the average mean firing rates (MFRs) evoked by stimuli applied in the preferred (P; ●) and nonpreferred (NP; ○) directions of motion at four different velocities (7.5, 12, 15, and 24 cm/s) before ("control" observations; A) and after injection of 500 μg/kg iv PCP (B). Figure 13, C and D, shows the average ITV (CV; ●) exhibited by the responses obtained in each direction of motion at each velocity, as well as the pronounced velocity dependency of this SI neuron’s directional sensitivity (Δ'v; ○).
because previous studies have emphasized the neuron-to-neuron consistency of the effects of changing a parameter of natural stimulation on neuronal variability. For example, Tolhurst et al. (1981, 1983), Vogels et al. (1989), and Zohary et al. (1994) reported the variance in the mean firing rate response of striate cortical neurons to increase proportionately with increasing stimulus contrast, and Levine (1994) observed that the variance in the mean firing rate responses of retinal ganglion cells and lateral geniculate neurons increases monotonically with increasing stimulus luminance.

Although prior studies did not systematically evaluate the effects of skin stimulus parameters on central somatosensory neuron intertrial response variation, Tolhurst et al. (1981, 1983), Vogels et al. (1989), and Zohary et al. (1994) reported the variance in the mean firing rate response of striate cortical neurons to increase proportionately with increasing stimulus contrast, and Levine (1994) observed that the variance in the mean firing rate responses of retinal ganglion cells and lateral geniculate neurons increases monotonically with increasing stimulus luminance.

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Mechanisms of SI neuron ITV

The experimental observations that invite mechanistic explanation are as follows: 1) $\text{CV}_{\text{SI}}$ is much greater than $\text{CV}_{\text{MRA}}$ (Fig. 3); 2) $\text{CV}_{\text{SI}}$ varies with the position of the stimulus within the RF (Fig. 7), being lowest at the RF center and increasing

![Fig. 11. Effects of PCP, ketamine (KET), and pentobarbital sodium (PB) on SI neuron CV and MFR.](http://jn.physiology.org/)
with distance from the RF center; 3) KET and PCP consistently reduce CV_{SI} (Figs. 9–11, also Fig. 13); 4) when stimulus velocity is increased within the 1- to 10-cm/s range of velocities, the values of CV_{sMRA} and CV_{SI} change in opposite directions (Fig. 3); and 5) NMDA receptor block with either PCP or KET causes some SI neurons to increase their mean firing rate (e.g., Fig. 11).

That CV_{SI} consistently is greater than CV_{sMRA} has a ready explanation: i.e., each additional synapse in the projection path from the skin receptor to SI neuron adds to the magnitude of intertrial response variation observed before drug administration (CV_{PRE}).

At the low dosages used in these experiments, both PCP and KET are known to selectively block NMDA receptors (Collingridge and Watkins 1994; Iversen et al. 1989; Lodge et al. 1989), and to selectively elevate the threshold for evoking SI neuron activity at off-center locations in the RF (Duncan et al. 1982; McKenna et al. 1982). These actions, together with the substantial evidence that somatosensory corticocortical influences are mediated predominantly by NMDA receptors that occur at highest density in layers II/III (Monaghan and Cotman 1985), whereas direct thalamocortical influences are mediated predominantly by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Fukada et al. 1998; Hagihara et al. 1988; Hicks and Conti 1996; Salt et al. 1995; Weinberg and Kharazia 1996; also Armstrong-James 1995; Armstrong-James et al. 1993; Fox et al. 1989, 1990; Nishigori et al. 1990; Shirokawa et al. 1989; Thomson et al. 1988, 1996) raise the possibility that PCP and KET reduce CV_{SI} by selectively reducing the influences conveyed via corticocortical connections. That is, PCP and KET may selectively eliminate the NMDA receptor–mediated influences of the relatively more variable, long-range corticocortical connections that convey activity evoked at off-center locations in the RF, and at the same time spare the AMPA receptor–mediated influences that are evoked from the RF center and conveyed by thalamocortical afferents (by means of direct monosynaptic connections, and also disynaptically via the spiny stellate cells of the same column).

In addition to reducing intertrial response variation, administration of PCP or KET frequently modified mean firing rate. Specifically, PCP increased MFR in the majority of SI neurons studied (Fig. 11, bottom left plot), and KET increased MFR in approximately half of the neurons studied (Fig. 11, bottom middle plot). This observation seems, at least at first glance, difficult to attribute to drug-induced block of NMDA receptors if one accepts the ideas that excitatory influences evoked at the RF periphery of an SI neuron are conveyed indirectly to pyramidal neurons via corticocortical connections, and that those influences are expressed through NMDA receptor activity (see preceding para-
response to that direct drive thus will not be maximal, but will be partially suppressed by lateral inhibitory influences deriving from the co-active columns that surround it. Therefore, under this condition (one presumed to approximate the condition of afferent drive evoked by application of a skin brushing stimulus to a neuron’s RF center), systemic administration of an NMDA receptor antagonist is expected to reduce lateral inhibitory influences (because these are attributable to glutamnergic corticocortical influences, and are mediated via NMDA receptors on local GABAergic interneurons that terminate synaptically on pyramidal neurons) on the pyramidal neurons of the directly activated column. In this way, systemic administration of either PCP or KET would permit full expression of the direct thalamocortical (AMPA receptor mediated) excitatory drive that reaches those pyramidal neurons during skin stimulation. The frequent, but usually relatively small, increases in MFR obtained with the relatively low doses of PCP and KET used in our experiments are regarded as consistent with this explanation.

Why is it that over the 1- to 10-cm/s range of stimulus velocities, $C_{V_{SI}}$ behaves differently than $C_{V_{MRA}}$ ($C_{V_{MRA}}$ increases monotonically with increasing stimulus velocity over the range 1–10 cm/s, but $C_{V_{SI}}$ declines over the same range; see Fig. 3)? The explanation we favor is that the negative slope of the $C_{V_{SI}}$ versus velocity relationship over the velocity range 1–10 cm/s is achieved by an action mediated by a particular set of intrinsic connections known to exist within SI cortex. More specifically, our view is that the influence on SI pyramidal neurons of corticocortical input is selectively attenuated by an intrinsic cortical inhibitory mechanism that leaves the direct input conveyed to pyramidal neurons from somatosensory thalamus (and expressed by AMPA receptors) unimpared.

How might this intrinsic inhibitory mechanism be achieved? A selective decrease in the influence of corticocortical input on SI pyramidal neurons (expressed by postsynaptic NMDA receptors) could be achieved via the double bouquet (DB) cells located within the same cortical column as the pyramidal cells. DB cells are very numerous in the upper cortical layers, and their axons descend radially through both the upper and middle cortical layers, making numerous GABAergic inhibitory synaptic contacts along the way (Jones 1975). The feature of DB cells that makes them especially interesting insofar as this mechanism is concerned is that, although their radially oriented axons make many synapses on the basal dendrites and also on the oblique side branches of apical dendrites of pyramidal neurons in the same column, the synapses made by DB axon terminals completely avoid the main shaft of the apical dendrites (DeFelipe et al. 1989; DeFelipe and Farinas 1992). As a result, DB cells may be able to powerfully and selectively attenuate (by membrane hyperpolarization and by electrotonic shunting) the contributions of synapses at distal locations on the basal and oblique dendrites to a pyramidal neuron’s spike discharge response to skin stimulation, while permitting synapses on the apical dendrite to remain fully competent in terms of their ability to influence the neuron’s spike discharge response to skin stimulation.

The idea that thalamocortical afferents appear to provide direct input to pyramidal neurons that is less variable than the input provided via corticocortical afferents, together with the above-described distinctive pattern of DB cell axonal arborization, led us to ask whether direct thalamocortical input might preferentially influence a pyramidal neuron via its apical den-
drite, while corticocortical input preferentially influences the cell via the basal/oblique dendrites. Because the neuroanatomic literature offers clear examples of thalamocortical and corticocortical axons terminating on pyramidal neuron basal dendrites and also on apical dendrites (Deuchars et al. 1994; Gabbott et al. 1987; Hornung and Garey 1981; McGuire et al. 1991), it seems very unlikely that the two types of inputs to SI pyramidal neurons terminate exclusively on either type of dendrite (see also Thomson et al. 1989). However, the existing evidence does not rule out the possibility that there might be quantitative differences in the termination of thalamocortical and corticocortical axons on the apical and basal/oblique dendrites of pyramidal neurons. Another aspect of cortical intrinsic connectivity that may be highly relevant to the possibility that the contributions of NMDA receptor–mediated corticocortical input to the stimulus-evoked response of SI neurons may be dynamically regulated is the pattern of termination of spiny stellate cell (SS) axons on pyramidal neurons. SS cells are located in layer 4 (Jones 1975; Lund 1984), are the major recipients of thalamocortical connections, and distribute their axons radially to pyramidal cells in the same cortical column. Because the axons of SS cells run parallel and in close apposition to the apical dendrites of pyramidal cells, they have the opportunity (and are widely believed) to form multiple, high-density excitatory synapses on the apical dendrites (Jones 1981; Lund 1984). The intrinsic connectivity described in this and the preceding paragraph is summarized schematically in Fig. 16. Although the pattern of synaptic termination of SS cell axons on SI pyramidal neuron apical dendrites described above and shown in Fig. 16 is consistent with the available evidence, it remains to be directly demonstrated.

The scheme of intrinsic connectivity shown in Fig. 16 would allow DB cells to selectively control the effectiveness of corticocortical inputs to pyramidal cells. To explain, consider the neural events set into motion on the delivery of a 10-cm/s stimulus to a discrete region on the skin. As detected in our recording experiments, a 10-cm/s stimulus evokes a vigorous (but submaximal) response in the sMRAs with an RF that falls within the stimulated skin region (Fig. 2), and the central projections of these sMRAs, in turn, provide strong drive to SI neurons (presumably both pyramidal and DB cells) that have an RF center that includes the stimulated skin site. The action

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**FIG. 15.** Velocity dependency of SI neuron direction and velocity discriminative capacity is altered by PCP. Example of SI neuron where PCP (300 μg/kg iv) increased mean firing rate and decreased trial-by-trial response variation for –1 h after the injection (A and B; dotted vertical line indicates time of PCP administration; flags indicate ±1 SD in mean firing rate; each point indicates mean firing rate response derived from the responses to 30 stimulus presentations). Neuron was studied before and at different times after PCP administration by applying brushing stimuli in opposite directions and at 2 different velocities (A, 5.6 cm/s; B, 14.2 cm/s) to the same path in the RF. Plots shown in C and D show the time course of the PCP effect on velocity discriminative capacity (velocity Δe; C) and on direction discriminative capacity (direction Δe; D).
FIG. 16. Intrinsic mechanisms enabling stimulus-directed modification of the magnitude of SI neuron intertrial response variation. Inhibitory synapses indicated by filled (black) presynaptic terminals; excitatory synapses by unfilled presynaptic terminals. Thalamic activity evokes SI pyramidal neuron (P) spike discharge activity primarily by activation of spiny stellate (SS) cells whose axons terminate synaptically on the P cell apical dendrite. P cell activation via this path is short latency and exhibits less trial-by-trial response variability than activation evoked via the less direct, corticocortical path. DB, double bouquet cell. Glutamnergic excitatory neurotransmission between terminals of SS cells on both P and DB cells is effected via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; glutaminergic transmission between terminals of corticocortical axons and P cells effected via NMDA receptors; DB cells inhibit P cells by presynaptic release of GABA. A decrease in the effectiveness of synapses located on the distal basal dendrites of P cells is proposed to accompany RF center stimulation at 10 cm/s. Under this stimulus condition, excitatory postsynaptic currents set up at glutamnergic synapses located at distal sites on the basal dendrites of P cells do not lead to effective depolarizing current flow through the spike initiating site in the initial segment region (these currents are opposed and shunted by the inhibitory currents in the proximal basal dendritic membrane caused by the action of GABA released from activated DB cell axon terminals). In addition, dendritic length constant may increase and membrane time constant decrease with the degree of stimulus-evoked P cell activation (Bernander et al. 1991; Holmes and Woody 1989); the former contributing to the decreased effectiveness of synapses located more distally on the basal dendrites; the latter causing a shift in P cell mode of operation from integrate-and-fire toward coincidence detection (Konig et al. 1996; Sejnowski 1995; Shadlen and Newsome 1994, 1995, 1998; Softky 1995; Softky and Koch 1993).

essential for achievement of the minimal SI neuron response variation observed in our experiments under this stimulus condition is that with relatively little delay, the activated DB cells in a strongly activated cortical cell column(s) trigger postsynaptic inhibitory currents in the pyramidal cells that reduce (by membrane hyperpolarization and via electrotonic shunting) the synaptic currents set up by active excitatory synapses located more distally on the basal and oblique dendrites. If this actually occurs, the result would be a substantial reduction of the contributions to the pyramidal neuron response of the glutamnergic corticocortical inputs coming from other less-activated (“off-focus”) cortical columns, because the major fraction of these inputs is targeted to distal sites on the basal and oblique dendrites. In contrast, the glutamnergic inputs from SS cells (because these inputs are relatively direct and exert a larger synaptic response than the corticocortical inputs, they should exhibit lower intertrial response variation) terminate principally on the main shaft of the neuron’s apical dendrite, and thus they, unlike the corticocortical inputs, should be unaffected by the dendritic inhibitory/synaptic current shunting actions associated with DB cell activity. By means of this mechanism, therefore, DB cell activation would reduce the strength of corticocortical input relative to the input arriving via direct thalamocortical afferents, and, as a result, the response variation of the pyramidal cells in the column(s) that receive direct stimulus-evoked thalamocortical input would be less than that observed under stimulus conditions when both corticocortical and thalamocortical connections contributed to the response.

A quite different outcome is anticipated when the brushing stimulus moves more slowly (e.g., at 1 cm/s); in this case the stimulus evokes much weaker activity in sMRAs and, as a result, only weak spike discharge activity in SI pyramidal and DB cells. The DB cells, because they are only weakly activated under this stimulus condition, exert a weak shunting effect on the basal/oblique dendrites of pyramidal neurons with the result that the glutamnergic activity conveyed by corticocortical axons (and expressed mainly by NMDA receptors) contributes significantly (relative to the contribution of corticocortical influences to the response to a 10-cm/s stimulus) to the spike discharge response of pyramidal cells. Moreover, because the corticocortical input to pyramidal cells is more variable than that provided by SS cell axons, the response of pyramidal neurons to a 1-cm/s stimulus is more variable from one stimulus trial to the next.

The situation is most straightforward at high stimulus velocities (velocities >10 cm/s), for at these velocities the period of time the stimulus remains in contact with the skin becomes the dominant factor. As was demonstrated in Fig. 1, the number of spikes evoked in both sMRAs and SI neurons by a moving stimulus decreases rapidly with increasing velocity because of the very brief time the stimulus remains in contact with the skin. As a result, the contribution of dendritic inhibition/shunting by DB cell axons to the SI magnitude of SI neuron intertrial response variation decreases progressively as velocity is increased over the range 10–100 cm/s.

To summarize, the observed decline of SI neuron response variation in the 1- to 10-cm/s velocity range is hypothesized to be attributable to a suppressive/inhibitory effect that the direct thalamic input to a cortical column exerts (via the GABAergic synapses of DB cells on the proximal basilar dendrites of pyramidal neurons; Fig. 16) on the corticocortical input to the basilar and oblique dendrites of pyramidal cells in that same column. Although the organization of cortical intrinsic connections suggests that this effect may be attributable to DB cell-mediated synaptic currents set up in the proximal basilar dendrites, the same or at least a similar effect might also be achieved by other means. For example, direct thalamocortical excitatory drive could also suppress the contributions of corticocortical input to pyramidal neurons by increasing dendritic membrane length constant (Bernander et al. 1991; Holmes and Woody 1989).
Contributions to somatosensory discriminative capacity

The velocity- and NMDA receptor dependency of SI neuron intertrial response variation demonstrated by the experiments of this study may account for what has been regarded as a discrepancy between human somatosensory perception and SI neuron behavior; that is, although human directional sensitivity on forearm hairy skin is optimal at velocities in the vicinity of 10 cm/s, and falls off progressively as velocity is increased or decreased (Essick and Whitsel 1985a,b), for most SI neurons the differences between the mean firing rates evoked by opposing directions of motion increases progressively over the entire velocity range (1–100 cm/s) used in the present study. The findings lead us to propose that the velocity tuning of cutaneous directional sensitivity principally is attributable not to the difference in SI neuron MFRs evoked by opposing directions of stimulus motion, but to the fact that SI neuron response variation is minimal at intermediate velocities (i.e., at velocities in the vicinity of 10 cm/s for neurons with RFs on forearm hairy skin). Furthermore, the evidence is consistent with the idea that the lowest SI neuron intertrial response variation (and the highest capacity for discrimination) occurs with stimulation of the RF center at velocities in the vicinity of 10 cm/s because this condition of skin brushing stimulation evokes a response to which NMDA receptor-mediated synaptic currents (and corticocortical inputs) contribute minimally.

In general, the findings are regarded as consistent with the emerging view that even at the earliest stages of cortical sensory information processing cells are highly mutable in their functional properties and process a much greater diversity of information than is conveyed via direct, short-latency thalamocortical connections (Armstrong-James 1995; Gilbert 1998; Lee and Whitsell 1992; Whitsell et al. 1989, 1991).

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