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Review

Dynamic representations of the somatosensory cortex

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ABSTRACT

Neural representation of somatosensory events undergoes major transformation in the primary somatosensory cortex (SI) from its original, more or less isomorphic, form found at the level of peripheral receptors. A large body of SI optical imaging, neural recording and psychophysical studies suggests that SI representation of stimuli encountered in everyday life is a product of dynamic processes that involve competitive interactions at multiple levels of cortical organization. Such interactions take place among neighboring neurons, among local groups of minicolumns, among neighboring macrocolumns, between SI and SII, between Pacinian and non-Pacinian channels, and bilaterally between homotopic somatosensory regions of the opposite hemispheres. Together these interactions sharpen SI response to suprathreshold and time-extended tactile stimuli by funneling the initially widespread stimulus-triggered activity in SI into the local group of macrocolumns most directly driven by the stimulus. Those macrocolumns in turn fractionate into stimulus-specific patterns of differentially active minicolumns. Thus SI dynamically shapes its representation of a tactile stimulus by selecting among all of its neurons initially activated by the stimulus a subset of neurons with receptive-field and feature-tuning properties closely matching those of the stimulus. Through this stimulus-directed dynamical selection process, which operates on a scale of hundreds of milliseconds, SI achieves a more faithful representation of stimulus properties, which is reflected in improved performance on tactile perceptual tasks.

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The long-term goal of the authors' research is to advance understanding of the cerebral cortical mechanisms which govern perception of tactile stimuli representative of those encountered in everyday life. The purpose of this review is to summarize recent experimental observations and describe methods we have developed to quantitatively assess the time- and space-dependencies of tactile perception in different subject populations. We attribute many of these dependencies to the dynamic character of the somatosensory cortical representation of tactile stimuli.

Much of the insight that has been previously gained into dynamic somatosensory cortical processes employed variations of receptive field mapping techniques. These approaches were used extensively to examine somatosensory cortical topographical organization. Briefly, the receptive field mapping observations obtained in these studies were interpreted to indicate that somatosensory cortical representations in adult subjects undergo topographic remodeling after a variety of experimental manipulations, including peripheral nerve transection, digit amputation, syndactyly, differential use of restricted skin surfaces and restricted cortical lesions (for review, see Merzenich, 1987). Receptive field mapping observations also serve as the basis for the claim that somatosensory topographic maps are not only use-dependent and use-modifiable throughout life, but also

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can be modified by alterations in behavioral state (Merzenich, 1987). This view of somatosensory cortical functional plasticity conflicted with prior beliefs that the adult neocortex was hard-wired, with its operations preshaped mainly by developmental processes. Rather, the ideas put forth by Merzenich and colleagues maintained that the basic processes underlying cerebral development (i.e., synaptic weight modification) continue to operate throughout life and retain the capacity to be influenced by experience. Thus, somatosensory cortical topographical organization can be thought of as continuously modifiable; that is, there "is an accumulated record of input histories within neocortical fields" that, in turn, determines the representational details of cortical maps (Merzenich, 1987). We view the work that we describe in this review as being consistent with and an extension of the previously described ideas of dynamic somatosensory cortical topographical organization.

In the first part of this review, we summarize some of the factors that influence cortical–cortical interactions in SI: the minicolumnar organization of somatosensory cortex, the interactions within SI that lead to convergence of afferent inputs, interactions between SI and SII, and the influence of ipsilateral inputs on activity in SI. Taking these different influences into account, we believe that SI is a node of a much larger extended network, and that we can perhaps better understand the influences of the overall network by delivering longer duration stimuli. The vast majority of previous studies of vibrotaction (both psychophysical and neurophysiological) have used near-threshold amplitudes and relatively short durations ($\leq$1 s) of sinusoidal skin stimulation. While there is certainly great utility in obtaining information about the CNS response to such stimuli, comprehensive understanding of the neural mechanisms involved in the processing of skin stimuli representative of those encountered in everyday life requires in-depth mechanistic understanding of the time-dependent modifications of the cortical responses which occur during long duration (>1 s) tactile stimuli. Our view is that the protocols a number of researchers currently use to evaluate tactile sensory performance lack the sensitivity and power required to detect and quantify the integrity of the primary somatosensory cortical neural mechanisms that enable the dynamic adjustments of sensitivity and resolution required for normal human tactile sensory performance. In subsequent sections, we describe the general influence of extended duration tactile stimuli on somatosensory cortex (and consequently perception), an example of the cortical dynamics that can be studied with extended duration stimuli, and finally, how we can better design sensory-based diagnostics utilizing such knowledge.

1. The role of the minicolumn in somatosensory information processing

In 1978, Mountcastle hypothesized that the smallest functional unit of neocortical organization (the "minicolumn") is a radial cord of cells about 30–50 μm in diameter, and that sensory stimuli activate local groupings of minicolumns called "macrocolumns" (Mountcastle, 1978). This hypothesis subsequently received support from multiple lines of experimental evidence, leading to its substantial elaboration.

Structurally, minicolumns are attributable to the radially oriented cords of neuronal cell bodies evident in Nissl-stained sections of cerebral cortex. It is likely that they also are related to ontogenetic columns (Rakic, 1988) and to the radially oriented modules defined by the clustering of the apical dendrites of pyramidal neurons (Peters and Yilmaz, 1993). Among the various elements of neocortical microarchitecture, *spiny-stellate* cells and *double-bouquet* cells (Jones, 1975, 1981; Lund, 1984) are most directly relevant to Mountcastle's concept of the minicolumn. Spiny-stellates are excitatory intrinsic cells that are especially prominent in layer 4 of primary sensory cortex. They are the major recipients of thalamocortical connections and, in turn, they (especially the star pyramid subclass of spiny-stellates) distribute afferent input radially to cells in other layers. Double-bouquet cells are GABAergic cells whose somata and dendritic trees are confined to the superficial layers. The axons of double-bouquet cells descend in tight 50 μm diameter bundles across layers 3 and 4 and into layer 5, making synapses along the way on the distal dendrites of pyramidal and spiny-stellate cells, but avoiding the main shaft of apical dendrites (DeFelipe and Farinas, 1992; DeFelipe et al., 1989; Jones, 1975, 1981). Because the double-bouquet cells are more likely to inhibit cells in adjacent minicolumns rather than in their own, they offer a mechanism by which a minicolumn can inhibit its immediate neighbors.

Because of the prominent differences in RF properties that exist among neighboring minicolumns in sensory cortex in adults, even the simplest sensory stimulus should evoke a spatially complex minicolumnar pattern of activity in the engaged cortical region—such a pattern consisting of a patchwork of active and inactive minicolumns (Favorov and Kelly, 1996; Tommerdahl et al., 1987, 1993). This expectation is in accord with experimental observations obtained in high-resolution 2-deoxyglucose (2-DG) metabolic studies of mouse (barrel field) and monkey SI (McCasland and Woolsey, 1988; Tommerdahl et al., 1987, 1993). Those studies revealed not only that the distribution of stimulus-evoked 2-DG labeling in somatosensory cortex is modular on a macrocolumnar scale, but is highly non-uniform within such a macrocolumnar module. Analysis of the spatial distribution of activity within the characteristic column-shaped patches of 2-DG label evoked in primary somatosensory cortex by natural skin stimuli suggested that such patches are made up of groupings of highly active minicolumns inter-digitated with less active minicolumns. More recent observations utilizing optical imaging techniques have also provided evidence of the emergent features of the functional minicolumn in sensory information processing (Chiu et al., 2005; Kohn et al., 1997; Tommerdahl et al., 2005a).

Most of the experimental literature that has addressed the topographical organization within the primary somatosensory, visual, auditory, and motor cortical areas (and association cortex as well) at high resolution shows that while neighboring neurons exhibit a remarkable uniformity from the standpoint of some RF property (e.g., stimulus orientation in visual cortex), they tend to differ prominently in other properties (for review see Favorov and Kelly, 1996). In fact, when sensory cortical neuron RF dimensions are considered, neighboring neurons typically have little in common—that is, a stimulus optimal for one cell frequently activates its neighbor much less effectively. A number of studies (Abeles and Goldstein, 1970; Albus, 1975; Favorov and Whitsel, 1988; Favorov and Diamond, 1990; Hubel and Wiesel, 1974) suggest, however, that this prominent diversity in the receptive field properties of neurons located in the same locale in sensory cortex is constrained substantially in the radial dimension—that is, cells that occupy the same radially oriented minicolumn have very similar RF properties. In other words, the tendency for the RF properties among neighboring sensory cortical neurons to be different is mainly attributable to the diverse RF properties of neurons that occupy neighboring minicolumns. Fig. 1 illustrates the minicolumnar organization of single neuron RF properties that published studies have identified within cat and monkey primary sensory cortex.

The above-described model of minicolumnar organization suggests that changing a stimulus position on the skin would not shift the response of the cortex somatotopically at minicolumnar resolution. Rather, as a stimulus moves across the skin, at macrocolumnar resolution, there would be a series of abrupt shifts between the cortical loci that are predominately active, but

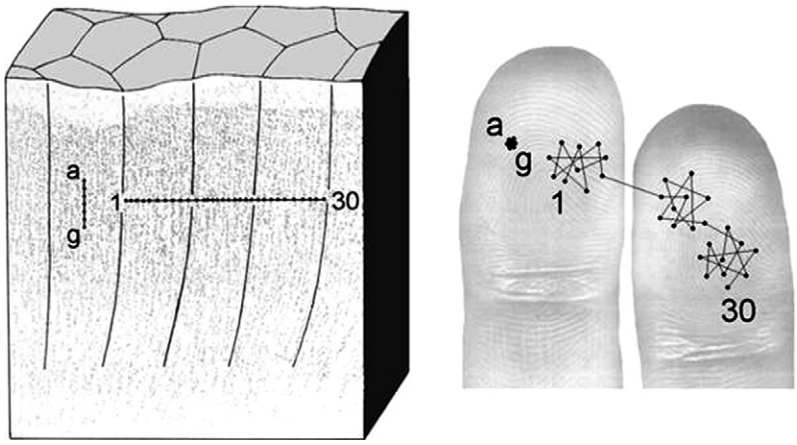

Fig. 1. Summary of minicolumnar RF organization in SI somatosensory cortex. Left: Drawing of cross-section of Nissl-stained cortical tissue showing darkly stained cell bodies organized in radially oriented cords, interpreted as minicolumns. Filled circles labeled *a–g*—sequence of neurons located within a single minicolumn; *1–30*—sequence of neurons located in series of adjacent minicolumns. Right: Sequences of RF centers (connected dots) mapped by neuron sequences *a–g* and *1–30*. Note that RF centers for SI neurons that occupy the same minicolumn stay close together, whereas the RF centers for pairs of neurons located in neighboring minicolumns shift back and forth over large distances, and occupy totally non-overlapping skin regions when the pair of neurons occupies different SI macrocolumns. Based on Favorov and Whitsel (1988) and Favorov and Diamond (1990).

the patterns within these loci would be very different. OIS imaging studies support this concept (Chiu et al., 2004, 2005), and thus, it appears that the emergent patterns that are formed by minicolumnar activation from repetitive stimulation could be an important factor in feature extraction (Chiu et al., 2005; Kohn et al., 1997; Tommerdahl et al., 1987, 1993). Thus, it would be anticipated that human subjects with abnormal minicolumnar structure would have altered sensory perception, and this is the case with autism. Autism subjects, who have a well above-normal density of minicolumns in parietal cortex (see Casanova, 2007 for recent review) are much better at spatial localization than healthy control subjects when the task is limited to brief stimuli (Tannan et al., 2006; Tommerdahl et al., 2007a). However, when stimulus duration is increased to 5 s and on the order that minicolumnar patterns become well defined in SI cortex in OIS imaging studies (Chiu et al., 2005), they do not exhibit an increase in performance. Healthy adults, on the other hand, demonstrated a nearly twofold increase in spatial localization ability with longer stimulus duration (Tannan et al., 2006; Tommerdahl et al., 2007a). These differences in improved tactile localization performance appear to reflect the deficit in short-range parietal corticocortical connectivity identified in subjects with autism by Casanova et al. (2006). Such changes in connectivity could lead to the imbalance in excitation and inhibition that underlies the neocortical hyperexcitability and unstable activity in cortical networks characteristic of autism (Polleux and Lauder, 2004; Rubenstein and Merzenich, 2003).

2. Convergence of vibrotactile inputs across "channels"

For many years, researchers have been aware of the possibility that large, extensively interconnected neural networks might behave in ways not predictable from the functional properties of the network's individual elements or from how the elements are interconnected. Interestingly, a significant body of human psychophysical research has been widely interpreted to indicate that: (i) information projected to SI over pathways activated by skin receptors tuned to low-frequency skin stimuli (i.e., the slowly adapting [SA] and rapidly adapting [RA] receptors) is, to a considerable extent, processed independently (and separately) from information that reaches SI over the pathways that convey afferent activity originating in skin receptors (PC: Pacinian Corpuscles) tuned to high-frequency stimulation and (ii) integration of these two very different types of information does not occur until levels of cortical information processing higher/later than primary somatosensory cortex (collectively, (i) and (ii) above constitute the "independent channels" hypothesis—see Bolanowski et al., 1994) for review). Recent observations in our lab – both neurophysiological and psychophysical – appear incompatible with the view that SI information processing involves little interaction between the information conveyed by the SA and RA channels until later stages of the CNS.

For examples, (1) a multi-second 200 Hz stimulus to the skin distal forelimb was shown to evoke a strong and persistent suppression/inhibition of the region in the contralateral SI dominated by input from RA-1 type skin mechanoreceptors (Tommerdahl et al., 1999a,b, 2005b) and (2) concurrent 200 Hz/25 Hz ("complex") stimulation of a skin site was shown to evoke SI activation substantially smaller than that evoked by "pure" 25 Hz stimulation of the same site (Tommerdahl et al., 1999a, 2005b). The reduction in spatial extent of the SI response to the complex stimulus led us to develop a relatively simple psychophysical test, and by extension, we made the observation that the complex stimulus, while reducing the spatial extent of the SI response, improved a human subject's tactile spatial acuity (Tannan et al., 2005a,b). Additionally, human psychophysical studies also suggested the perceptual relevance of the 200 Hz-evoked suppression/inhibition of the SI response to 25 Hz stimulation of a skin site we observed in our animal studies—the human studies showed that although frequency discrimination is enhanced when the frequency of an adapting stimulus is the same as the frequency of the standard stimulus, discriminative capacity decreases to levels well below-normal when the frequencies of the adapting and standard stimuli are very different (Tommerdahl et al., 2005c).

A series of experiments (Tommerdahl et al., 2005b) was carried out to evaluate the contralateral SI response to continuous 25 Hz vs. 200 Hz stimulation (a) at multiple skin sites arranged along the proximal–distal axis of the fore- or hindlimb; (b) in the presence and absence of a vibration-squelching ring placed in firm contact with the skin surrounding the stimulus site; (c) before and after topical application of local anesthetic to the stimulus site; and, finally, (d) to continuous 25 Hz or 200 Hz stimulation applied independently, and also concomitantly ("complex waveform stimulation") to the same skin site (Tommerdahl et al., 1999a, 2005b). The principal findings were as follows: (a) the relationship between the SI optical responses to 25 Hz vs. 200 Hz stimulation of

a skin site varies systematically with position of the stimulus site on the limb—at a distal site both 25 Hz and 200 Hz stimulation evoke a well-maintained increase in absorbance, and when the stimulus site is shifted proximally on the limb the response to 200 Hz, but not the response to 25 Hz stimulation, converted to a decrease in absorbance; (b) placement of a ring about a skin site at which in the absence of a ring 200 Hz stimulation evokes a decrease in SI absorbance converts the response to 200 Hz to a response consistent with increased SI RA neuronal activation (i.e., with the ring in place 200 Hz stimulation evokes a change in SI absorbance that closely resembles the response to 25 Hz stimulation); (c) topical local anesthetic preferentially and reversibly decreases the magnitude of the absorbance increase associated with 25 Hz flutter stimulation; and (d) complex waveform stimulation consistently is associated with a smaller increase in absorbance than that obtained with same-site 25 Hz stimulation. Collectively, these findings are viewed as consistent with the idea that the Pacinian (PC) afferent activity which unavoidably accompanies cutaneous flutter stimulation triggers CNS mechanisms that "funnel" (sharpen) the spatially distributed contralateral SI response to the flutter stimulus. Viewed in this context, the fact that a flutter stimulus unavoidably co-activates RA and PC afferents appears functionally beneficial because the CNS mechanisms activated by PC afferent drive modify the SI response to skin flutter in a manner predicted to enable more accurate perceptual localization than would be possible if the flutter stimulus only activated RA afferents. Insofar as physiological relevance is concerned, the authors' view is that the cortical (and perceptual) effects of vibrotactile stimuli delivered in the *absence* of a vibration-squelching ring/surround are directly relevant to the issue of the role of convergence in somatosensory information processing—that is, the cortical (SI–SII) effects of high frequency skin stimuli encountered in the course of active manual exploration of tactile objects. On the other hand, stimuli delivered in the presence of a ring/surround have cortical and perceptual effects unrepresentative of those evoked by the high frequency skin stimuli encountered in normal, everyday life.

A number of experiments that recorded optical intrinsic signal (OIS) imaging and/or single neuron responses of SI to 25 Hz and 200 Hz stimuli reported that whereas the SI optical and neuronal responses to flutter (25 Hz) stimulation are robust and sustained over time, the responses to vibration (200 Hz) are transient (Tommerdahl et al., 1999a, 2005b; Whitsel et al., 2001, 2003). Extracellular responses of almost every SI RA neuron/neuron cluster sampled using extracellular spike train recording methods was robust, well-maintained, and well-entrained to the stimulus when the frequency of stimulation was 25 Hz, whereas entrained spike discharge activity to 200 Hz stimulation was evident only when the microelectrode encountered neurons within the usually very small SI region that displayed a sustained increase in absorbance during 200 Hz stimulation. The spike train recordings also demonstrated that although RA neurons located in adjacent SI cell columns may react in a very similar way to flutter stimulation, their responses to high-frequency stimulation of the same skin site can be very different. These results demonstrated that for the RA neurons in the highly localized region that undergoes a transient increase in absorbance during 200 Hz stimulation mean firing rate (MFR) (1) increases transiently shortly after stimulus onset, (2) collapses to a near- or below-background level and remains either at below background or at near background levels for as long as the 200 Hz stimulus continues, and then (3) elevates ("rebounds") transiently upon stimulus termination (for full description of these results, see Whitsel et al., 2001).

We interpret the above-described results to indicate that while the response of contralateral SI during the initial ($\leq$1 s) period after onset of suprathreshold high-frequency skin stimulation closely mirrors the increased activity such a stimulus evokes in RA skin afferents, with continuing stimulation responsivity of the neurons in the same region of SI becomes suppressed/inhibited due to a change in the balance of stimulus-evoked activities directed to the middle *vs.* upper layers via thalamocortical and corticocortical connections, respectively. In addition, we consider it likely that the above-described mechanism underlies the "across-channel" effect on frequency discriminative capacity demonstrated in human psychophysical studies (Tommerdahl et al., 2005c). That study showed that high frequency skin stimulation degrades the perceptual capacity to discriminate frequency of skin flutter stimulation. This finding is regarded as consistent with the proposal (Giese, 1999) that mammalian sensory systems cannot usefully be decomposed into multiple modules that are relatively independent and studied separately, but must be considered as systems in which functionally important interactions occur between channels even at early levels of the sensory projection paths. In addition, the described optical imaging and neurophysiological recording studies of SI strongly suggest that appreciation of the contributions to somesthesis of the massive systems of intrinsic and corticocortical connections will only be achieved in experimental studies that use conditions of vibrotactile stimulation that effectively engage those connections.

At first glance, the above-described studies seem directly at odds with the often-cited conclusions that the integrity of the channels that mediate vibrotaction (i.e., the PC and RA afferents and their projection targets in the CNS) "remains intact ... at all levels of the nervous system" (Gescheider and Verrillo, 1982). In other words, according to this view, no interaction occurs between RA- and PC-mediated afferent inputs at all levels of the CNS up to and including primary somatosensory cortex. Our OIS imaging and the human psychophysical findings of Gescheider and Verrillo appear compatible when one takes into account the fact that the psychophysical results were obtained using a stable ring surround that eliminates the lateral spread of vibration through the skin (and, therefore, much of the PC afferent drive evoked by 200 Hz stimulation), used very brief stimulus durations (typically 20 ms; relative to the 500 ms to 1 s of continuous stimulation required for vibration to produce significant suppression of SI responsivity in our experiments), and exclusively utilized near-threshold vibrotactile stimuli. Indeed, our perspective is that the published human psychophysical results support our discovery that with a ring/surround in place, a 200 Hz/30 μm skin stimulus produces an SI activation pattern strongly resembling that evoked by same-site 25 Hz stimulation—presumably reflecting the considerable RA afferent activation and the minimal PC afferent activation expected (Whitsel et al., 2000) under this condition of stimulation. It should also be considered that the prolonged exposure of the skin to continuous vibrotactile stimulation ("vibrotactile adaptation") at either 25 Hz or 200 Hz is accompanied by a *differential* modification of human frequency discriminative capacity. More specifically, whereas a 15 s pre-exposure of a skin site to 25 Hz or 200 Hz adaptation was found to improve human frequency discriminative capacity at frequencies identical or similar to that of the adapting stimulus (Goble and Hollins, 1994), substantial impairment of frequency discrimination occurred at frequencies very different (i.e., at frequencies that evoked a qualitatively distinct sensory experience) than the frequency of the adapting stimulus (Tommerdahl et al., 2005c).

3. How does activity in SII impact activity in SI?

For many years it has been recognized that SII consists of multiple areas that can be distinguished on the basis of functional and cytoarchitectonic criteria (Fitzgerald et al., 2004, 2006; Mountcastle, 2005; Robinson and Burton, 1980; Robinson, 1973;

Whitsel et al., 1969). While the existence of these subdivisions of SII has been interpreted as consistent with the existence of "multiple distributed hierarchical processing streams" (Fitzgerald et al., 2004) similar to those identified in the visual system, and with the proposal (Caselli, 1991, 1993; Friedman et al., 1986; Mishkin, 1979; Murray and Mishkin, 1983, 1984) that dual streams for somatosensory information processing exist in each hemisphere – a ventral stream involving SII concerned with object recognition, tactual learning and memory; and a dorsal stream involving SI concerned with somesthetic spatiotemporal function – the contributions of the various subdivisions of SII to somatosensory perception is not well understood.

OIS imaging studies carried out in our lab (Favorov et al., 2006; Tommerdahl et al., 1999b, 2005e) yielded the initially surprising finding that the magnitude and time course of the SI and SII responses to stimulation of a contralateral skin site are similar for certain modes of stimulation (i.e., 25 Hz skin flutter) but are very different for other conditions (i.e., 200 Hz skin vibration). The responses of individual SI and SII pyramidal neurons have been evaluated extensively in both monkeys and cats (Coleman et al., 1999; Ferrington and Rowe, 1980; O'Mara et al., 1988; Rowe et al., 1996a,b; Tommerdahl et al., 1999a,b; Whitsel et al., 2001) and the results appear generally consistent with the above-described OIS imaging results. More specifically, the SI RA neuron excitatory response to high-frequency stimulation is strikingly transient: the great majority of neurons that continue to be activated by continuous 25 Hz stimulation of a skin site fail to maintain an elevated level of spike discharge activity for more than 100–500 ms after onset of 200 Hz stimulation at that same site; and in many such neurons spike firing rate drops to levels well below-background. In contrast, many SII neurons exhibit above-background activation for relatively much longer periods of stimulation of the RF (Ferrington and Rowe, 1980; Kawakami et al., 2001; Morley and Rowe, 1990). In addition, OIS imaging studies demonstrated that high frequency skin vibration routinely reduces SI activity to below-background levels (Tommerdahl et al., 1999a,b). And finally, the above-described multiple and prominent differences between the global optical and single neuron responses we obtained in our studies of SI and SII appear compatible with the following neuroanatomical observations: First, in SI the axons of thalamocortical afferents that convey information arising in PC mechanoreceptors terminate preferentially in the superficial cortical layers; second, in SII the thalamocortical afferents relaying information arising in PC afferents and those thalamic afferent conveying information arising in RA mechanoreceptors terminate extensively in the middle cortical layers (Craig, 1996; Jones, 1998; Jones et al., 1978; Rausell et al., 1992; Rausell and Jones, 1991a,b); and third, the available evidence indicates that PC input to SII exceeds that to SI, and SII neurons exhibit higher levels of entrainment to high-frequency stimulation than do SI neurons (Mackie et al., 1996; Rowe et al., 1996a).

In order to directly compare the SI–SII response to single-site contralateral flutter vs. vibration, OIS imaging was used to evaluate the response evoked in the contralateral primary somatosensory receiving areas (SI and SII) of anesthetized cats by either 25 Hz ("flutter") or 200 Hz ("vibration") stimulation of the central pad on the distal forepaw (Tommerdahl et al., 1999b). In that study, 25 Hz stimulation evoked an absorbance increase in a region in both contralateral SI and SII. 200 Hz stimulation of the central pad consistently evoked a substantial absorbance increase in contralateral SII, but little or no absorbance increase in contralateral SI. In contrast, 200 Hz central pad stimulation usually evoked an absorbance decrease in the same contralateral SI region that underwent an increase in absorbance during same-site 25-Hz stimulation. The stimulus-evoked absorbance changes in contralateral SI and SII were shown to be significantly correlated during vibrotactile stimulation of the central pad—positively during 25 Hz stimulation but negatively during 200 Hz stimulation (see Fig. 2). These findings suggest that 25 Hz central pad stimulation evokes spatially localized and vigorous neuronal activation within both SI and SII in the contralateral hemisphere, whereas although 200 Hz stimulation evokes vigorous and well-maintained activation within the contralateral SII, its principal effect on the contralateral SI is inhibitory (for full details, see Tommerdahl et al., 1999b). A number of additional findings are not easily accommodated with the idea that the PC-type SI neurons that encode the frequency of skin stimulation over the range which humans experience as vibration. First, Mountcastle et al. (1969) demonstrated in their elegant initial study of the cortical mechanisms in flutter-vibration that neither the overall mean firing rate nor any periodic ordering

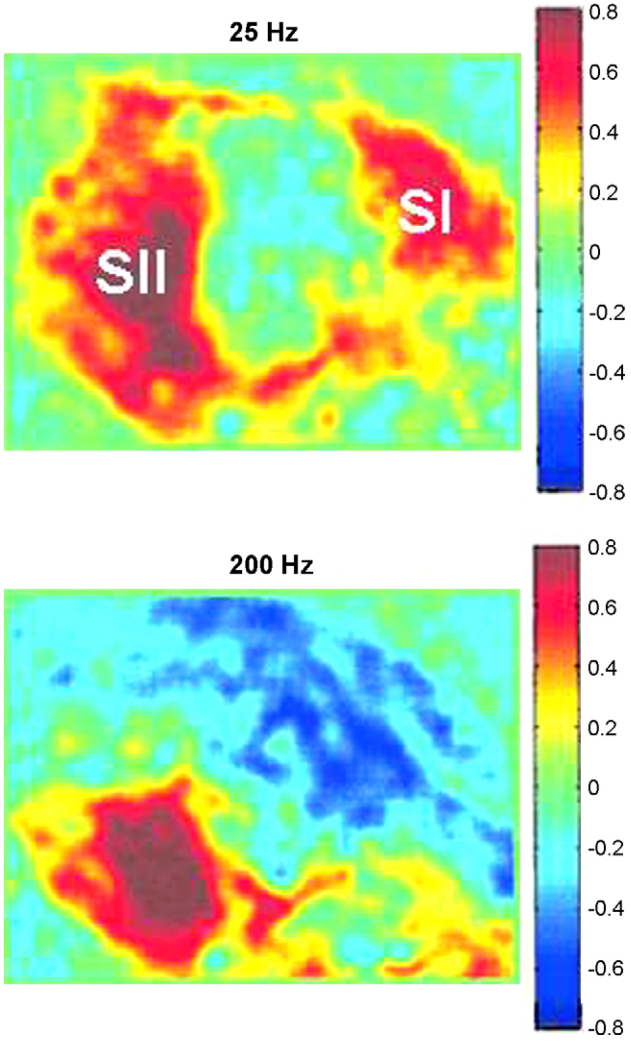

Fig. 2. Correlation maps generated from OIS-imaging data obtained from the same subject with 25 Hz vs. 200 Hz stimulation. *Top*: obtained from the data acquired under 25-Hz stimulation; *bottom*: obtained from the data acquired under 200-Hz stimulation. Color scale (*right*) indicates the value of the correlation coefficient. Each map was obtained by computing the correlation (estimated by the correlation coefficient, *r*) between the changes in absorbance over time at each pixel location and the time course of the increase in average absorbance within the SII boxel that exhibited the maximal absorbance increase during the delivery of the appropriate stimulus frequency. Note that under the 200-Hz stimulus condition, the activity in most locations in the SI forelimb region is anti-correlated with the time course of the absorbance change that the 200-Hz stimulus evokes in the maximally activated boxel within SII—see *bottom*; whereas under the 25-Hz condition, the activity at most sites in both SI and SII is positively correlated with the time course of the absorbance change that the 25-Hz stimulus evokes within the maximally activated SII boxel (*top*). Modified from Tommerdahl et al. (1999a).

of the spikes discharged by PC-type SI neurons provides a discriminable signal of frequency at stimulus frequencies between 100 Hz and 200 Hz. Second, Lebedev et al. (1994) reported that during the delivery of 127 Hz stimulation to the contralateral palm the mean firing rate (MFR) of SI neurons in conscious behaving monkeys is significantly lower than the firing rates evoked at 27 and 57Hz—a finding that led Lebedev et al. (1994) to conclude that the "decrease in MFR of neurons with cutaneous RFs at 127 Hz may be due to inhibitory mechanisms dependent on stimulus frequency." Third, in cats, high-frequency (200 Hz) skin stimuli have been reported to activate SII neurons far more effectively than SI neurons (McIntyre et al., 1967; Rowe et al., 1985). Fourth, a number of neuroimaging studies have found that low vs. high frequency stimuli differentially activate SI and SII (Francis et al., 2000; Harrington and Hunter Downs, 2001). The differential response of SI and SII to flutter vs. vibration is consistent with the concept of parallel processing of tactile information in SI and SII—an idea which has been expanded on significantly by Rowe and colleagues (Coleman et al., 1999; Murray et al., 1992; Rowe et al., 1996a,b; Turman et al., 1992, 1995; Zhang et al., 1996, 2001).

4. Is there an ipsilateral influence on SI?

Recently, dual-site stimulation experiments in which the ipsilateral mirror-image body site was stimulated simultaneously with the contralateral site stimulus revealed that ipsilateral stimulation influences the response of SI to contralateral stimulation (Tommerdahl et al., 2005d, 2006). Interestingly, the results showed that the SI response to bilateral stimulation was less than that observed when only the contralateral site was stimulated. This outcome, together with (1) our observation that stimulation of the ipsilateral thenar evokes an increase in absorbance in the SI hand representational region (Tommerdahl et al., 2006), (2) reports by others of neurons with ipsilateral receptive fields in the hand region of SI of non-human primates (Iwamura et al., 2002), (3) demonstrations of short-latency activation of human SI in response to electrical stimulation of the ipsilateral median nerve (Allison et al., 1989a,b, 1992; Korvenoja et al., 1995; Nihashi et al., 2005), (4) repeated demonstration in human psychophysical studies (Braun et al., 2005; Craig, 1985; Craig and Qian, 1997; Essick and Whitsel, 1988; Harris et al., 2001; Tannan et al., 2005b) of a precisely somatopically organized interaction of information evoked from body sites on opposite sides of the body midline, and (5) the recent demonstration that a unilaterally applied flutter stimulus evokes short-latency neuromagnetic activation in both the contralateral and ipsilateral SI of conscious humans (Tan et al., 2004), strongly suggest that SI is activated via a hitherto underappreciated, extensively spatially distributed, but highly organized afferent connectivity that links SI with skin regions on both sides of the body midline. At least to date, the functional meaning of this extensive afferent connectivity remains uncertain.

The above-described results conflict fundamentally with the still widely held concept of the hand representational region in SI as a "contra-only" information processing network. The importance of this set of observations is that it requires significant expansion of the limited dimensions of the extent of the skin region conventionally considered to provide afferent drive to cell columns within the forelimb representation of SI. Specifically, optical imaging results obtained from SI of cats and monkeys revealed unambiguously that stimulus-evoked activation of mechanoreceptors located in regions as distant as sites on the *ipsilateral* hand influence the response of the SI forelimb representational region to stimuli applied to the contralateral hand (Tommerdahl et al., 2005e, 2006). Such observations not only show that mechanoreceptor inputs from skin regions on *both* sides of the body midline contribute to the information processing capacities of even a local region within SI (e.g., the region of SI that represents the hand), but they make it clear that assessment of the functional implications of such a spatially extensive afferent connectivity of a local SI region will require detection and thorough characterization of the influences that different modes of ipsilateral skin stimulation exert on the SI response to stimulation of a contralateral skin site.

The observations reported in published human imaging studies raise the possibility that ipsilateral input may exert some type of modulating effect on SI. Interestingly, however, the different laboratories/investigators who have addressed this issue have detected very different effects of ipsilateral input on the SI response to contralateral stimulation. For example, Schnitzler et al. (1995), using MEG, has shown that tactile stimulation of the ipsilateral hand *enhances* the response of the primary somatosensory cortex to electrical stimulation of the contralateral median nerve. Conversely, Korvenoja et al. (1995) reported that the SI activation (detected using MEG) evoked by electrical stimulation of the contralateral median nerve is *suppressed* during movement of the fingers of the ipsilateral hand, and Staines et al. (2002) report that the SI activation (measured using fMRI) evoked by passive bilateral stimulation is weaker than the activation evoked by passive unilateral stimulation. These observations from human imaging studies raise the intriguing possibility that the SI response to a contralateral stimulus may be modulated in opposite ways when the mode, site and/or timing of the ipsilateral and contralateral stimuli are same *vs.* different. Relevant to this issue are findings obtained in a recent investigation (Pluto et al., 2005) in which inhibitory influences on SI arising from the opposite hemisphere were suppressed by block of both $GABA_A$ and $GABA_B$ receptors—findings that have been regarded as "... evidence for active suppression of irrelevant communication within one cerebral hemisphere originating from the contralateral hemisphere ..." (Woolsey, 2005). We view the available evidence somewhat differently: that is, although some information arising from the opposite hemisphere and reaching SI may turn out to be irrelevant to somesthetic perception, the effects on SI of ipsilateral stimuli that we and others have observed to date are reproducible and highly sensitive to stimulus conditions resembling those encountered in the course of bimanual tactile object exploration. As a result, our position is that the available evidence does not enable definitive conclusions about the impact of these effects on SI information processing, and that the significance of such SI modulation for somatosensory perception could be considerable.

One significant aspect of ipsilateral input to SI is that it raises a number of questions about the validity of a number of experimental paradigms commonly in use that assume that any input to the ipsilateral hand in the primate is insignificant in the recording of contralateral activity in primary somatosensory cortex. Although the activity evoked by ipsilateral stimulation may seem insignificant, it does appear to have a prominent effect on the cortical response to contralateral stimulation. An experimental protocol that makes the assumption that ipsilateral input is insignificant could be introducing an enormous amount of experimental variability. For example, in the case where primates receive a stimulus to right hand (while restrained) and press buttons with the left hand while recording responses in the left hemisphere (such as the protocols described in (Luna et al., 2005; Romo et al., 1998, 2000), we would predict that the freely moving non-restrained hand could impact the cortical activity evoked by the test stimulus delivered to the contralateral hand. How much of an impact ipsilateral stimulation would have in such a behavioral protocol is difficult to predict, but it could account for some of the differences that have been observed between delivering vibrotactile stimuli to primates in which both hands were restrained and those obtained when a freely moving hand could potentially

generate stimulus-dependent activity in SI of the hemisphere that is being studied.

5. Extended exposure to stimulation

An extended exposure to continuous vibrotactile stimulation (“vibrotactile adaptation”) at a discrete skin site not only elevates absolute detection threshold at that site, but decreases the subjective magnitude of stimuli with physical attributes similar to those of the adapting stimulus (Bensmaia and Hollins, 2000; Burton et al., 1998; Gescheider et al., 1979, 2004; Hollins et al., 1990, 1996; Wedell and Cummings, 1938). Although the neural mechanisms that underlie these effects of a pre-exposure to vibrotactile stimulation on perception remain to be established with absolute certainty, multiple animal studies have demonstrated that such a pre-exposure is reliably accompanied by reductions in neuronal responsivity at both peripheral and central levels of the somatosensory nervous system. For example, such stimulation is accompanied by a sustained decrease of the responsivity of skin mechanoreceptors located in the vicinity of the stimulated skin region (Leung, 1995; Leung et al., 2005), a long-lasting depression of the responsivity of neurons in the cuneate nucleus of the brainstem ipsilateral to the stimulus site (O’Mara et al., 1988), and a persisting reduction in the spatial extent of the SI region that responds to mechanical stimulation of a discrete skin site (Leung, 1995). Although appreciation of the neural mechanisms remains incomplete, it has become apparent that the perceptual effects of vibrotactile adaptation are not, as early workers believed (Verrillo et al., 1969), attributable solely to peripheral receptor “fatigue”/desensitization. The clearest examples of this have been provided by Goble and Hollins (1994) and Tommerdahl et al. (2005c) who showed that adaptation to a vibrotactile stimulus results in significant improvement of the capacity of subjects to discriminate between vibrotactile stimuli that differ only in frequency when the frequencies of the adapting and standard stimuli are similar, and as indicated in preceding paragraphs Tommerdahl et al. (2005c) showed that when the frequencies of the adapting and standard stimuli are very different, human vibrotactile discriminative capacity is degraded following adaptation. These different (opposite) effects of adaptation on human vibrotactile discriminative performance are notable because optical imaging and neurophysiological recording studies in cats and monkeys have reported that the region of contralateral cerebral cortex (SI) widely believed to be essential for normal frequency discriminative performance is influenced in different (essentially opposite) ways by a prolonged exposure to low- *vs.* high-frequency vibrotactile stimulation. Specifically, although SI remains activated (and presumably, therefore, fully responsive) for the full duration of 25 Hz stimulation, it undergoes a profound suppression/inhibition within 1–2 s of the onset of 200 Hz stimulation (Tommerdahl et al., 1999a,b; Whitsel et al., 1999, 2000, 2001). The adaptation-induced impairment of human vibrotactile frequency discrimination reported by Tommerdahl et al. (2005c) is regarded as fully consistent with the idea that antagonistic interactions (“cross-channel interactions”) can and frequently do occur between the CNS processes triggered by activity in the ascending projections of both the RA-1 (also referred to as FAI) and PC (FAII) mechanoreceptive afferents.

Optical intrinsic signal (OIS) imaging in vivo studies carried out in our lab provided evidence that even short-duration skin stimuli evoke an intrinsic signal which remains evident in somatosensory cortex (in both SI and SII) for an extended period (typically, 5–15 s) after stimulus termination (Tommerdahl et al., 2002; Tommerdahl and Whitsel, 1996). Initially, we regarded this very slow decay of the OIS as having little or no physiological significance. This interpretation proved premature, however, because in vitro studies carried out in parallel with our in vivo studies (Kohn et al., 2000; Lee et al., 2005) revealed that the OIS, while providing an accurate indication of the locus and magnitude of local neuronal activation, is not directly attributable to neuronal activity. Instead, our studies of spinal cord and sensorimotor cortical slices convincingly revealed that the OIS is the result of astrocytic swelling due to uptake (along with water) of the excess extracellular K+ and neurotransmitters (e.g., glutamate) released during excitatory neurotransmission. Accordingly, the slow decay of the OIS reflects the slow dissipation of the reduced extracellular space that accompanies astrocyte swelling. Recognition of the basis of the OIS is highly relevant to the studies of cortical information processing because if, in fact, the OIS identifies the region in which extracellular space is reduced, the responsivity of neurons in that region also should be modified (increased). Thus, the spatio-intensive pattern of activity detected by the OIS imaging method can be regarded as a map that predicts the locus, magnitude, and sign (+/−) of the cortical neuronal response alteration evoked by a skin stimulus. More recently, Moore and Cao (2007) have proposed that hemodynamics also play a role in information processing through the modulation of neural activity both by direct and indirect mechanisms—the indirect mechanism most notably through the regulation of astrocytic activity.

6. Amplitude dependence of SI response to skin flutter

One of our recent experimental goals was to determine how stimulus amplitude is encoded by SI cortex (Simons et al., 2005, 2007). In those studies, OIS imaging was used to study the responses evoked in the contralateral SI of anesthetized squirrel monkeys by 25 Hz sinusoidal vertical skin displacement stimulation. Stimulation of a discrete skin site on the forelimb evoked a prominent increase in absorbance within the forelimb representational region in cytoarchitectonic areas 3b and 1. Each increase in stimulus amplitude (varied from 50 μm to 400 μm) led to a proportional increase in the magnitude of the absorbance increase in the responding region of areas 3b and 1 while surrounding cortex underwent a decrease in absorbance (see Fig. 3). Correlation maps revealed that as stimulus amplitude was increased, the spatial extent of the activated SI region remained relatively constant, but the activity within this activated region increased progressively. Additionally, as stimulus amplitude was increased, activity in the surround of the activated SI territory decreased, suggesting increased inhibition of neuronal activity within these regions. The increase in absorbance was proposed to be accompanied by a progressive increase in the firing rate of neurons in the activated SI region (as described by Whitsel et al., 2001, 2003). The relatively constant spatial extent of this stimulus-evoked increase in SI absorbance suggests that the reason an increase in the amplitude of a 25 Hz skin stimulus does not lead to a larger area of SI neuronal activation is due to an amplitude-dependent lateral inhibitory effect that spatially funnels the responding SI neuronal population. These findings are consistent with more recently reported neuroimaging and neurophysiological studies (Chen et al., 2007; Muniak et al., 2007).

In addition to our discovery that vibrotactile flutter stimulation of a skin locus at different amplitudes evokes an optical response that is spatially constrained in the same local region of SI, we characterized the impact of flutter amplitude on the spatial pattern of activity evoked within the responding SI region (Chiu et al., 2005). In order to characterize the pattern of activity within the responding SI region, images of the response were segmented and analyzed using spatial frequency analysis. The analysis revealed that: (1) characteristic spatial frequencies in the optical intrinsic signal emerge within the responding SI region within 3–5 s of stimulus onset; (2) the stimulus-evoked optical activity is spatially

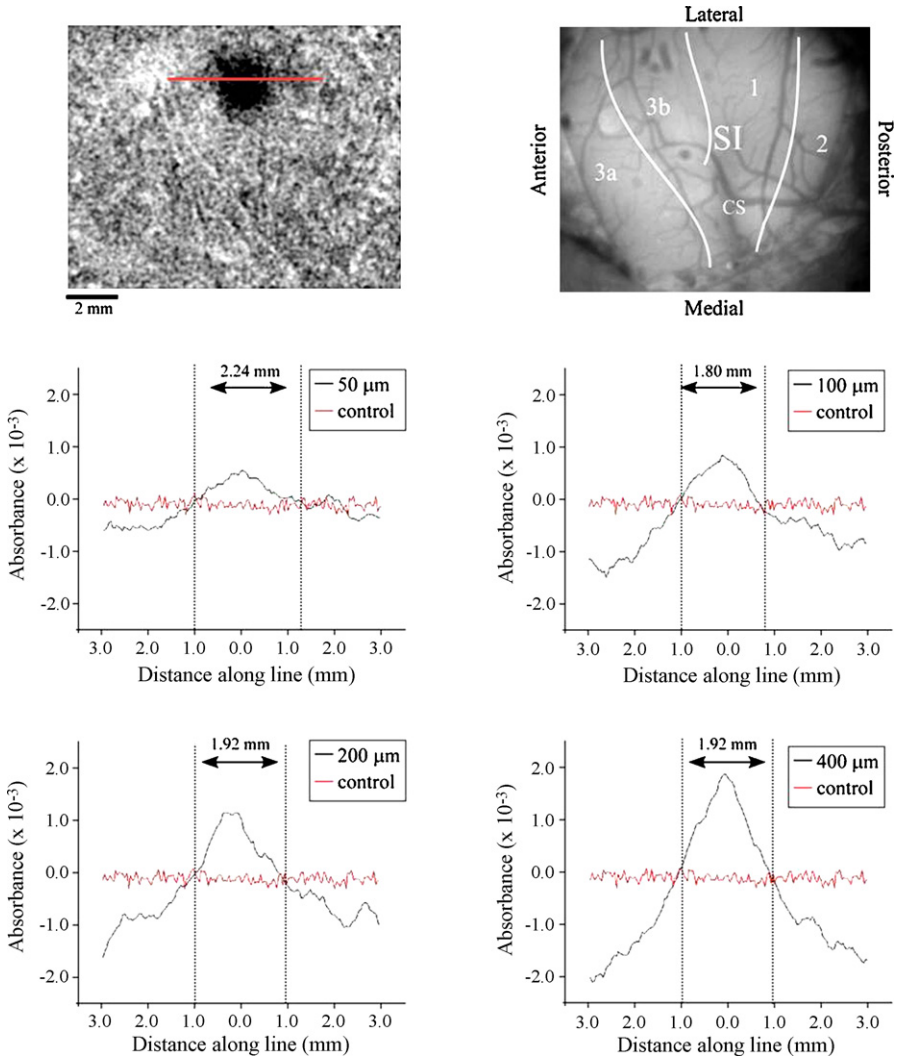

Fig. 3. Spatial histograms of activity at different amplitudes. Absorbances were measured at each amplitude along the red line shown in the OIS image at top left. Each plotted value represents an average of pixels spanning 100 μm above and below the line and a distance of 40 μm along the line (bin size was 40 μm × 200 μm). The control condition is plotted on each graph to indicate "background" levels absorbance. Dashed lines on plots indicate where stimulus-evoked activity crosses background absorbance levels (indicating the boundaries of above background absorbance). Histograms indicate no significant change in cortical territory displaying above background absorbance with respect to stimulus amplitude. Higher amplitude stimulation produces regions of below-background absorbance directly outside of the regions of above-background absorbance. Modified from Simons et al. (2005).

organized in a form of several roughly parallel, anterior-posteriorly extended waves, spaced ~0.5 mm apart; (3) the waves exhibit spatial periodicities along their long axis; and (4) depending on stimulus amplitude, these within-wave periodicities range from fine 0.15 mm "ripples" at 50 μm amplitude to well-developed 0.5 mm fluctuations at 400 μm. The observed spatio-intensive fractionation on a *sub-macrocolumnar* scale of the SI response to skin stimulation was suggested to be the product of local competitive interactions within the stimulus-activated SI region and may be a feature that could yield novel insights into the functional interactions that take place in SI cortex (Chiu et al., 2005). If the competitive interactions that take place between minicolumns leads to the SI cortical pattern that could account for improvements in discrimination that have been observed with repetitive stimulation (Goble and Hollins, 1993; Tannan et al., 2007b; Tommerdahl et al., 2005c), then it would be anticipated that any change in neural circuitry that would lead to a reduction in the competitive interactions between cortical ensembles – at the macrocolumnar or sub-macrocolumnar scale – would result in a loss of those improvements. Such could be the case with autism subjects, who demonstrate a competitive imbalance between excitation and inhibition (Rubenstein and Merzenich, 2003) and demonstrate a lack of improvement with adaptation in amplitude discrimination tasks (Tommerdahl et al., 2007a).

7. Designing effective measures of sensory dynamics

The Nobel prize winning work of von Bekesy first introduced the concept of lateral inhibition playing a major role in the nervous system (Von Bekesy, 1965). Bekesy was unclear as to the exact mechanisms, but he described – using measures of sensory perception – the concept of lateral inhibition in all of the sensory systems. This concept led to the practical use of simple neurological measures such as "two-point discrimination" to be commonly used. To summarize, when two-points are placed closely on the skin, they feel as though they are one point. Move the points farther apart, and at some critical distance (two-point threshold), they are perceived as two-points. Different parts of the body (based on innervation density) have lower two-point thresholds (i.e., detecting two-points close together on the finger tips is easier than on the foot). Although later animal experimentation showed that cortical mechanisms in primary sensory

cortex were involved in such two-point discriminative tasks, the test itself was limited for several reasons. First, administration of the test is subjective and requires some skill (it is relatively easy to apply one tip before the other, and thus change the result). Second, the answer that a subject gives requires a certain amount of integrity (the subject always *knows* that there are two points). And third, because of the brevity of the stimulus, the test itself does not fully activate all the cortical mechanisms that are normally engaged with natural tactile stimulation. For example, studies in a laboratory setting by Vierck and Jones (1970) demonstrated that two-point discrimination improved when the two probe tips touching the skin were gently vibrated. This improvement was predicted, and later shown to be highly correlated (in animal studies) to changes in SI cortex mediated by dynamic cortical-cortical interactions evoked by repetitive vibrotactile skin stimuli (Whitsel et al., 1989, 1991). Additionally, it was predicted from these animal studies that cortical dynamics would lead to improvements in a discrimination task when the stimulus duration was lengthened, and that this improvement would be predominantly accounted for by the NMDA receptor system (Lee and Whitsel, 1992; Tommerdahl et al., 1993; Whitsel et al., 1989, 1991). Subsequently, other researchers tested this hypothesis and found that adaptation (or conditioning stimuli) did, in fact, improve a human subject's ability to discriminate between stimuli of differing amplitudes although adaptation did increase a subject's threshold (Goble and Hollins, 1993). While this was a very successful study, it was not a test that was easily applied to a large and/or diverse subject population, primarily for technical reasons: first, the study utilized a large, non-portable (single skin site) stimulator and thus restricted the study to subjects with access to a lab setting, and second, because of stimulator limitations, the study utilized a methodology that was prohibitively long and cumbersome. The use of a multi-site vibratory stimulator would allow us to address questions that had been initially conceptually framed by von Bekesy (i.e., how does lateral inhibition of two closely spaced stimuli affect perception?; also see Essick and Whitsel, 1988) and continued with the research conducted by those described previously in this review, who principally undertook addressing questions about the time-dependent evoked cortical response to a variety of modalities and sub-modalities of single-site skin stimulation. The device that we designed and fabricated to conduct such experiments is portable, lightweight and can be used in a variety of non-laboratory settings, and it consists of two independently controlled stimulators which allow delivery of stimuli simultaneously to two distinct skin sites with different amplitude, frequency and/or phase (for full description, see Tannan et al., 2007a). The methods that the device enables has allowed us to initiate more direct investigations of somatosensory information processing strategies that are employed when multiple cortical ensembles are activated in precise temporal and spatial relationships. For example, we recently demonstrated that synchronized conditioning stimuli – which serve to temporally link spatially proximal cortical ensembles – significantly impacts temporal order judgment (Tommerdahl et al., 2007b). More importantly, these novel methods could be applied to the study of neurologically compromised subjects that have undergone some type of systemic alteration in cortical function – either for developmental or degenerative reasons (Tommerdahl et al., 2007a, 2008) – and could give clinical researchers and/or physicians important information for the diagnosis and treatment of these subjects.

8. Conclusions

The diverse studies reviewed here form a basis for our "selectionist" view of SI cortical function. That is, we view SI as an information-processing network that responds to skin stimulation by selecting a *subset* among all of its neurons initially activated by the skin contact with the stimulating object. Our presumption is that this selected subset of SI neurons provides a more faithful representation of the object properties to the next stages of neocortical information processing than does the much larger – and "noisier" – SI population that responds initially to the stimulus.

We regard this "stimulus-directed" dynamic selection process to require participation of three systems of cortical connections:

- The first system is the afferent connections. These feed-forward connections give SI neurons their receptive fields and feature-tuning properties, but – in the absence of other influences – would not enable fine discriminative somesthetic perceptual performance, because they trigger stimulus-evoked activation of an excessively large SI neuron population.
- The second system is the intracortical lateral connections. These connections promote competitive interactions within SI that reduce the size of the responding SI neuronal population by dynamic constriction of the initial SI response towards the position in the SI topographic map that most closely reflects stimulus location on the skin and by dynamic fractionation of the spatial pattern of response *within* that cortical region.
- Finally, the third system is the feedback projections from higher-level cortical areas. These connections can either bias SI neuron responsivity in anticipation of afferent drive or, under ambiguous stimulus conditions, help in the selection of neurons that will represent the stimulus.

According to our selectionist view, when stimulus conditions are used that are simple and well defined, the initial SI response very rapidly is transformed by influences contributed by cortico-cortical and feedback connections to a response that accurately reflects stimulus attributes. Under complex and less well-defined conditions of skin stimulation, however, the SI response must undergo a temporally extended period of transformation before a response emerges that adequately represents stimulus attributes.

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