Axonal Processes and Neural Plasticity. II: Adult Somatosensory Maps

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Following our recent presentation of an axonal process sprouting and retraction framework for ocular dominance column formation, we now apply it, unchanged, to address issues of adult somatosensory map plasticity. Specifically, we model the rearrangement of S-I in adult rodents following denervation of a row of vibrissae, and the rearrangement of area 3b in adult monkeys following hyper-stimulation of a digit. While we do not attempt to capture the rapid changes which occur as the result of unmasking or potentiating existing connections, we demonstrate that axonal process sprouting and retraction is a possible mechanism mediating many of the long-term changes induced by anomalous peripheral activity. A significant feature of our framework, demonstrated by this study, is that it can account for plasticity in both developing and mature systems, and in different sensory modalities. In contrast, synapse-specific Hebbian models with synaptic normalization, which employ anatomically fixed connections capable of changes in efficacy, may not be able to account for both developmental and adult plasticity without the form of the imposed normalization, which enforces competition between afferents, being changed.

Introduction

The adult somatosensory cortex exhibits considerable plasticity (e.g. Kaas, 1991). First, in monkeys, the central portion of area 3b is devoted to an orderly representation of the glabrous surface of the hand (Merzenich et al., 1978). Following amputation of a digit, the cortical territory formerly innervated by it becomes responsive to neighbouring digits (Merzenich et al., 1984), and hyper-stimulation of a finger results in the expansion of its cortical territory (Jenkins et al., 1990). Second, in rodents, the trigeminal field consists of discrete aggregates of cells known as barrels (Woolsey and Van der Loos, 1970), each being innervated by one vibrissa (Welker, 1976). Selective damage to the nerve bundle innervating one row of vibrissae induces the expansion of the cortical territory of the flanking rows (Kossut et al., 1988; Welker et al., 1989). This change is associated with an increased expression of the growth-associated protein GAP-43 (Dunn-Meynell et al., 1992).

Normal postnatal barrel development seems to be independent of neural activity. Following infra-orbital nerve blockade from birth with tetrodotoxin (TTX) (Henderson et al., 1992) and postnatal blockade of cortical activity by TTX (Chiaia et al., 1992), normal barrel development occurs. Cortical application of 2-amino-5-phosphonovaleric acid (APV) does not prevent normal development, but plasticity in response to perturbations is inhibited (Schlaggar et al., 1993). The activity-independence of barrel formation is probably due to the topographical precision of the thalamocortical projections (Agmon et al., 1995). However, prenatal activity-dependent formation has not been conclusively ruled out.

At least two mechanisms appear to underlie adult somatosensory map plasticity. First, since some changes are rapid, or indeed immediate, this indicates that they are the result of potentiating existing connections. For example, immediate changes may be understood to be the result of removing inhibitory connections (Alloway et al., 1989), and ineffective synapses may be unmasked and become the dominant input to a neuron following deactivation of the formerly major input (Wall, 1977). Second, axon sprouting is strongly suggested in adult barrel plasticity. Given the precision of thalamocortical projections into the barrel field and the absence of neonatal activity-dependence in normal development, it is probable that barrel expansion could only occur by sprouting—there are not, apparently, any connections capable of being unmasked. Moreover, the increased expression of GAP-43 following denervation suggests the induction of sprouting. Also, the only plausible explanations of major reactivations of the cortex following deafferentation of a complete forelimb is axon sprouting (Pons et al., 1988).

Compared to the number of theoretical studies of developmental plasticity in the visual cortex (e.g. Legendy, 1978; von der Malsburg, 1979; Miller et al., 1989; Montague et al., 1991; Goodhill, 1993), there have been few such studies of adult plasticity in the somatosensory cortex. Pearson et al. (1987) applied Edelman’s theory of neuronal group selection (Edelman, 1987) to model the development and plasticity of finger maps, while Benuskova et al. (1994) applied the Bienenstock-Cooper-Munro theory (Bienenstock et al., 1982) to model changes in the adult barrel cortex. Both assume that plasticity is accommodated by changing synaptic strengths in an anatomically fixed network. Synapse-specific Hebbian models which impose synaptic normalization, however, may have difficulty in accounting for the plasticity of sensory maps at various stages of development. This is because different forms of normalization may be required.

In the visual cortex, for example, ocular dominance columns form during a critical period in development (Hubel and Wiesel, 1962). To account for their formation in the presence of inter-eye image correlations, subtractive synaptic normalization (so that \( s_i \rightarrow s'_i = s_i - t \), where the \( s_i \) are synaptic strengths and the constant \( t \) is such the \( \Sigma s'_i = N \), with \( N \) being the normalization constant) must be used in synapse-specific Hebbian models (Goodhill and Barrow, 1994; Miller and Mackay, 1994). Once a mature pattern of ocular dominance emerges, simulated deprivation has no effect, since in regions controlled by one eye, the other eye’s synaptic strengths have typically gone to zero. Such zero-strength connections should be regarded as having retracted (Antonini and Stryker, 1993). While the absence of plasticity of mature ocular dominance columns is required for consistency with experiment, subtractive normalization may be inappropriate when modelling adult somatosensory maps, since they should continue to exhibit plasticity. To maintain plasticity in them, it seems to be necessary to use multiplicative...
normalization instead (so that $s_i \rightarrow s'_i = N s_i / \Sigma s_i$). However, multiplicative synaptic normalization does not permit the development of ocular dominance columns except in the presence of inter-eye image anti-correlations (Goodhill and Barrow, 1994; Miller and Mackay, 1994).

Since normalization is imposed to model competition between afferents, this conflict presents a serious difficulty. However, given that competition is intimately connected with neurotrophic support, which influences sprouting and retraction (e.g. Purves, 1988), it is possible that a sprouting and retraction model could avoid this problem. In a previous paper we developed a sprouting and retraction framework, based on competition for neurotrophins, for the computational modelling of ocular dominance column formation (Elliott et al., 1996). We now apply it, unchanged, to the problem of modelling long-term adult somatosensory map plasticity. Specifically, we shall consider plasticity in the adult rodent barrel field following deafferentation of a row of vibrissae, and plasticity in adult primate finger maps following hyper-stimulation of a digit.

The plan for the rest of the paper is as follows. We first summarize our framework; for a more extensive discussion see Elliott et al. (1996). Next we present simulation results. Finally, we discuss our results.

Materials and Methods

In this section we outline the differences between the approach taken for modelling the connections between the lateral geniculate nucleus and the visual cortex in our previous work (Elliott et al., 1996) and that taken for modelling the connections between the relevant thalamic nuclei [the ventral posteromedial nucleus (VPMN) for the trigeminal system, and the ventral posterolateral nucleus (VPLN) for the somatosensory system] and the somatosensory cortex to be studied here.

We take the VPMN and VPLN to be regular, two-dimensional $s \times s$ arrays of $s^2$ cells each. For simulating finger maps, the VPLN will be partitioned into 25 blocks of cells arranged as a $5 \times 5$ square array, with one block of cells representing one vibrissa (a 'barreloid'). The somatosensory cortex is a regular, two-dimensional $c \times c$ array of $c^2$ cells. Periodic boundary conditions are enforced on all sheets. Each thalamic cell projects topographically to an $a \times a$ square arbor region on the cortex.

An energy function is constructed and minimized exactly as before (Elliott et al., 1996), and we continue to study both the relocation model and the interchange model. We restrict our attention to the simulation of quenched systems (i.e. with the temperature set to zero always) since simulated annealing does not produce qualitatively different results.

As with simulating deprivation in the visual system (Elliott et al., 1996), we must hand-set changes in response to anomalous peripheral activity in the somatosensory system. Thus, following deafferentation of whiskers we must permit their barreloids to retract all their processes from the cortex. This must be accompanied by compensating sprouting by flanking whiskers' barreloids into the vacant cortical space. Following hyper-stimulation of a finger we must permit its VPLN slice to sprout new processes which claim part of the cortical territory controlled by neighbouring fingers. While such hand-setting is unsatisfactory, we do not regard it as a significant problem in our study. By uncoupling sprouting and retraction in our models, it is possible to eliminate such hand-setting, but we do not discuss this here.

Results

We now discuss simulations of deafferentation- and hyper-stimulation-induced plasticity in adult somatosensory maps. First we present results for adult rodent whisker barrel plasticity, then results for adult primate finger map plasticity.

Whisker Barrel Plasticity

While it appears that whisker barrel development is activity independent (Henderson et al., 1992; Chiaia et al., 1992), for computational convenience we suppose that their development is activity dependent. This allows us easily to set up a mature map with barrel-like patterns. It is only the activity-dependent plasticity of the mature barrels which interests us here, so how we construct the mature map is unimportant. However, if it should transpire that prenatal activity-dependent segregation occurs in the trigeminal system of rodents, then our models shows that axonal sprouting and retraction is a possible developmental mechanism.

A regular $3 \times 3$ array of VPMN cells is devoted to each vibrissa, so that the VPMN is a regular $15 \times 15$ array partitioned into 25 barreloids. Each VPMN cell initially projects to a $9 \times 9$ square arbor region on the cortex. The cortex is a regular $31 \times 31$ array of cells. A whisker's barreloid is randomly activated with all other barreloids inactive and 10 000 axonal process updates permitted. Such large numbers of updates are allowed for reasons of computational convenience only. After ~25 stimulations per whisker, the afferents have segregated into clearly defined groups, each group representing one whisker.

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**Figure 1.** Simulated whisker denervation in the relocation model. The left map shows the normal, mature barrel field. The right map shows the result of simulated denervation of the middle row of whiskers. Each black region represents cortical territory controlled by one whisker, while the white regions represent uninnervated cortical cells. The parameters are: $c = 31$, $s = 15$, $a = 9$, $u = 32$. 

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We take the parameters for the thalamic and cortical arrays as five parallel slices, each containing an array of 3 x 15 VPLN cells. The developmental construction of the segregated map is well-innervated whisker barrels. These regions are an artefact of the way in which we generate the map. Reduction of the arbor region size, we have also increased \( u \) to \( u = 36 \), this being the smallest permitted value. Digits D1-D5 are represented in order as we move across the cortex. As for the simulation of whisker barrels, we find that the boundaries separating different finger representations are poorly innervated. In the right map, we hyper-stimulate digit D3 from the left map and permit some expansion of its territory into that controlled by adjacent digits. That is, we suppose that the hyper-stimulated finger's VPLN slice sprouts new processes which compete for and gain control of some of the territory controlled by digits D2 and D4.

The Relocation Model

In the left map of Figure 2 we show the simulated segregated barrel cortex. As we have increased the arbor region size, we have also increased \( u \) to \( u = 36 \), this being the smallest permitted value. Digits D1-D5 are represented in order as we move across the cortex. As for the simulation of whisker barrels, we find that the boundaries separating different finger representations are poorly innervated. In the right map, we hyper-stimulate digit D3 from the left map and permit some expansion of its territory into that controlled by adjacent digits. That is, we suppose that the hyper-stimulated finger's VPLN slice sprouts new processes which compete for and gain control of some of the territory controlled by digits D2 and D4.

Discussion

Our models appear to predict that the plasticity associated with somatotopic rearrangement of the mature barrel field depends on activity-dependent segregation of new processes, and therefore may be blocked by such factors as APV (Schlaggar et al., 1993). However, a slow advance of the cortical territory controlled by flanking whiskers is equally possible, in which case activity-dependent segregation would be unnecessary. It is possible that APV may still block such plasticity, so it may be difficult, experimentally, to distinguish between these two alternatives, without following explicitly the remodelling of terminal arbors.

We have assumed that a direct correlate of denervation of a row of whiskers is that the whiskers' barreloids retract all their terminal arbors. However, it would be necessary to assume that no such retraction occurs. Furthermore, it would
also appear to be necessary to assume that spontaneous activity associated with the damaged whiskers is well correlated.

In the relocation model we found that poorly innervated boundaries separate different finger representations. We do not know of any anatomical evidence which supports or refutes the existence of such boundaries. The physiological data, however, clearly rule them out, since it is known that somatotopically inappropriate connections exist but are inhibited, and that these connections may be unmasked (Wall, 1977; Alloway et al., 1989). However, if we increase the correlations between finger strokes—so that, for example, two adjacent fingers are occasionally stroked simultaneously—then the poorly innervated boundaries will not form so sharply. In contrast, the interchange model produces a roughly continuous shift in receptive fields as one traverses a finger boundary, even for single finger strokes.

In our previous work on the development of the visual system (Elliott et al., 1996), we stressed the role of neurotrophins in competition between afferents. Indeed, our framework was constructed so as to take these data into account. Since we wish to maintain the neurotrophic interpretation of our framework, we are therefore committed to the view that neurotrophins play an important role in the construction and maintenance of somatosensory maps. Recent results indicate that this may be possible. Prenatal injection of nerve growth factor disrupts the formation of whisker-related structures in the brain stem (Henderson et al., 1994). This result is similar to the observed desegregation of ocular dominance columns in kittens following infusion of brain-derived neurotrophic factor (Cabelli et al., 1995). Also, given the role of the N-methyl-D-aspartate (NMDA) receptor in regulating neurotrophins (Zafra et al., 1991; Gwag and Springer, 1993), the finding that mice lacking functional NMDA receptors fail to develop appropriate brain stem structures (Li et al., 1994) is suggestive.

In conclusion, we have shown that our approach to sprouting and retraction and competition for neurotrophins can account for the plasticity of adult somatosensory maps, in addition to the development of maps. Future work will include the uncoupling of sprouting and retraction, and attempts to account for the detailed dendritic morphology of cortical maps in the visual and somatosensory cortices. Preliminary indications suggest that these two problems are connected.

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