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The influence of post-nerve injury survival duration on receptive field size: Location, location, location

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Abstract

In the present study, we examined the relationship between post-injury survival duration and receptive field size at multiple levels of the ascending somatosensory neuroaxis. In experimentally naïve subjects, receptive fields on the glabrous hand are typically restricted to single digits. Yet, following targeted nerve section, receptive fields often span multiple digits. In these experiments, adult squirrel monkeys were subject to paired transections of the median and ulnar nerves and permitted to survive for varying periods (2–28 months) prior to terminal electrophysiological recording. The frequency of cutaneously activated multiple-digit receptive fields was evaluated in regions of brainstem, thalamus and cortex normally devoted to the (now) partially deafferented hand. We report that for area 3b of primary somatosensory cortex, receptive field size became smaller as a function of survival duration. In contrast, survival duration had no appreciable effect on the frequency of multiple-digit receptive fields in either the cuneate nucleus of the brainstem or the ventroposterior lateral nucleus of the thalamus. These observations suggest that the mechanisms responsible for the refinement of receptive fields are, primarily, resident to the cortex.

Keywords: VPL; Topography; Cuneate; Thalamus; Somatosensory; Reorganization

Over the past two decades, the observation of continued malleability of the central nervous system across the lifespan has gained considerable support (cf. [30]). The seminal experiments of Merzenich et al. [23,24] were among the first to convincingly demonstrate plasticity in the adult nervous system. Their observations that the somatotopic representation of the body surface in the adult primate brain is capable of dramatic reorganization subsequent to nerve injury demonstrated quite clearly that the concept of a developmental critical period for nervous system organization required revision.

Since those early experiments, considerable effort has been devoted to understanding the mechanisms, location and timing of injury-induced reorganization of central maps. Reports on the role of neurotransmitter systems [9,12,13,25,32], brain regions [22,26,27,31,34,35] and the temporal progression of this phenomenon [4,5,24] have made it increasingly clear that cortical reorganization cannot be explained by a single mechanism acting at a specific brain locus. While delineation of injury-induced reorganization has focused, in large part, on cortical maps, changes in receptive field topography at the level of the brainstem and thalamus have been documented as well (e.g., [3,10,35]). In fact, what might be considered a cortico-centric bias has been challenged by a growing body of research with an emergent theme suggesting that the dynamic organization of somatotopic maps is a product of interactive mechanisms operating across multiple levels of the neuroaxis. Still, respectful of the role of higher-order mechanisms, a central issue to be resolved is determining if changes in cortical topography are simply a reflection of subcortical modifications or if altered receptive fields in the brainstem and thalamus are mediated via corticofugal influences. The answer is likely a combination of both bottom-up [10,15,19] and top-down mechanisms [6,31,36].

Injury-induced changes in receptive fields occur seemingly simultaneously across multiple levels of the neuroaxis [7]. Our group, and others, has recently reported that the extent of reorganization immediately following nerve injury is greater in the cuneate nucleus (CN) of the brainstem than in the ventroposterior nucleus of the thalamus (VPL) and likewise greater in thalamic regions than in primary somatosensory cortex (area 3b) [3]. Yet, regardless of brain region, novel receptive fields detected

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during the early stages of reorganization are typically much larger than those observed pre-injury. For example, the representation of the intact glabrous hand in primary somatosensory cortex is characterized by receptive fields that are confined to a single digit, and indeed, only a small portion of that digit (e.g., [29]). Following peripheral deafferentation, however, receptive fields often span multiple digits, particularly at short survival durations post-injury (e.g., [11]). There is evidence to suggest that the cerebral cortex may play a unique role in shaping receptive fields both intracortically and in a corticofugal manner, and that receptive field size is influenced by post-injury survival duration (cf. [2,6,20]). In the experiments reported below, we evaluated the effect of post-injury survival duration on the incidence of multiple-digit receptive fields at the level of brainstem, thalamus and cortex. We hypothesized that mechanisms unique to the cortex might facilitate rapid refinement of receptive fields, compared to subcortical areas, and this property would be reflected in an inverse relationship between post-injury survival duration and receptive field size in the cortex, but to a much lesser extent in subcortical areas.

Adult squirrel monkeys (*Saimiri sciureus* or *Saimiri boliviensius*) were socially housed with food and water available ad libitum. In 15 animals, the median and ulnar nerves to one hand were transected following the principles of animal care detailed in NIH publication no. 86–23. The local institutional animal care and use committee approved all procedures prior to initiation of any experiments. Briefly, monkeys were anesthetized with an intramuscular injection of a mixture of ketamine hydrochloride (25–30 mg/kg) and xylazine (0.5–1.0 mg/kg). Their forearms were shaved and prepared for surgery with alternate scrubbings of povidone-iodine and alcohol. Under sterile conditions, an incision was made along the midline of the ventral forearm, the median and ulnar nerves were located by blunt dissection and cut about midway between the elbow and wrist. The epineural sheath of the proximal stump was retracted 0.5–1.0 cm and the exposed nerve avulsed. The empty epineural sheath was re-extended, folded back and ligated. The nerve stumps were repositioned and the incision closed with sutures. Post-surgically, all subjects received injections of penicillin, dopram hydrochloride and dexamethasone.

Subjects were permitted to recover for at least 2 months (range: 2–28 months) before terminal mapping of the affected brain regions. This period has been shown sufficient to permit complete reorganization of the hand representation in cortical area 3b [11]. For electrophysiological recordings, subjects were anesthetized as described above and placed in a stereotaxic frame. The scalp was reflected and dura overlying the targeted regions removed. Warm silicone gel was applied to prevent desiccation and the area normally devoted to the (now) partially deafferented hand was mapped at the level of the cuneate nucleus, VPL or 3b. Multi-unit recording techniques were used to map the affected regions and receptive fields were determined by gentle stimulation of the skin surface using fine probes and brushes. Upon completion of electrophysiological recordings, subjects were euthanized and brain tissue processed for a variety of purposes including procedures to confirm that recordings were in the intended target structures.

Subsequent to a survival duration that previously has been shown to permit complete reclamation of the affected somatosensory area, the hand representation in the brainstem, thalamus and cortex was mapped. In an attempt to maximize the amount of data collected from each animal, multiple levels of the neuroaxis were frequently mapped for each animal. The median number of penetration sites for brainstem, thalamus and cortex were 120, 106 and 83, respectively. At these extended survival durations, we report that the affected regions were completely reorganized and responsive exclusively to stimulation of the dorsal surface of the hand and digits in a roughly topographic manner. As a gross measure of receptive field size, we then assessed the frequency of multiple-digit receptive fields, an observation that does not typically occur in naïve subjects. We report that the frequency of multiple-digit receptive fields in area 3b of primary somatosensory cortex decreased systematically as post-nerve injury survival duration increased ($r = -.779$, $p < .01$; see Fig. 1). In contrast, receptive field sizes in VPL and cuneate nucleus did not change appreciably as survival duration increased following peripheral nerve injury ($r = .073$ and $.082$, respectively, $p > .05$). Comparing the regression lines indicated that as a function of survival duration, the frequency of multiple-digit receptive fields in the cortex was statistically different from the brainstem [$F(2,8) = 5.4592; p < .05$], but not thalamus. Brainstem and thalamic regression lines were not statistically different as a function of survival duration. Interestingly, even when only data from the first 15-month period are analyzed for cortex (to make direct comparison between regions), the regression equation suggests a marginal effect ($r = -.677$, $p < .10$) which is dramatically different from that observed for brainstem and thalamus at comparable survival durations.

In these experiments, we assessed the frequency of multiple-digit receptive fields as a gross measure of receptive field size

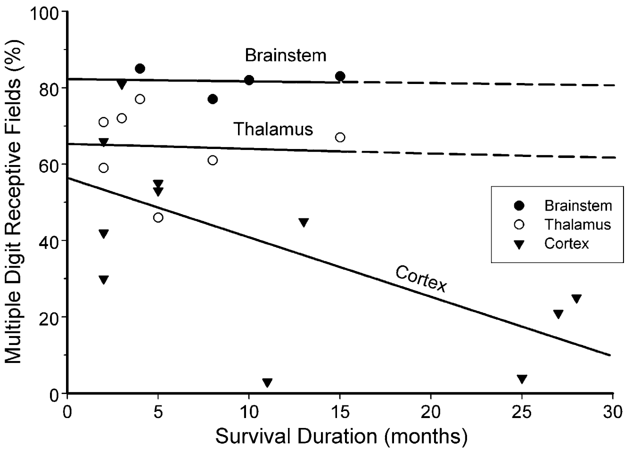

Fig. 1. The frequency of multiple-digit receptive fields is plotted as a function of survival duration subsequent to denervation of the glabrous hand. For both brainstem and thalamus, the regression lines have been extrapolated beyond the 15-month survival duration for visual comparison to comparable periods obtained for cortex. Regression analyses indicate that for primary somatosensory cortex, receptive field size shrank over time ($r = -.779$, $p < .01$). In contrast, in both brainstem ($r = .082$) and thalamic ($r = .073$) regions there were no appreciable changes in the frequency of multiple-digit receptive fields across the time sampled.