REORGANIZATION OF SOMATOSENSORY CORTEX SUBSEQUENT TO DORSAL COLUMN INJURY: A STUDY OF THE MARMOSET AND THE SQUIRREL MONKEY.

BY

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Psychology

August, 2011

Nashville, Tennessee

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For my grandmother,

a quiet, dignified woman.

ACKNOWLEDGEMENTS

This work would not have been possible without the financial support of the Christopher and Dana Reeve foundation, and for this I thank them.

I would like to thank my advisor Jon Kaas for his support and for his many words of wisdom. He is truly an inspirational man.

I thank my committee members Troy Hackett, Sohee Park, and Ford Ebner for their guidance and helpful discussion.

I thank Laura Trice for her histological prowess, and Mary Feurtado, our very own monkey whisperer.

I thank my lab mates, my family, and my friends for their support and guidance.

Many thanks to Halo and Olegovich ,a steady source of laughs,

& thank you Oleg, you have been wonderful.

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INTRODUCTION

Tactile processing is localized to the postcentral gyrus.

As intricate a mosaic as the cerebral cortex is, it was understandably a daunting and difficult task to identify and localize the components of sensory function. As early as 1902, a series of works aimed at doing just this began via investigation of the brain's surface morphology, histological detail, and connectional circuits (Smith et al, 1902; Campbell et al, 1905; Brodmann et al, 1909; Carlson et al, 1990).

By correlating patterns of cortical projections of specific thalamic nuclei with cytoarchitectonic divisions and sulcal repetitions, initial functional subdivisions of the somatosensory cortex were identified, all before common implementation of electrophysiological methods. Subsequent studies by Penfield et al (1937) revealed the sensory homunculus that lay just caudal to the central sulcus. These researchers were able to perform this great feat via electrical stimulation in awake patients undergoing surgical retraction for the treatment of epilepsy. Once somatosensory processing had seemingly been localized to the postcentral gyrus, efforts were intensified to parse and further subdivide functional somatosensory loci.

Based on findings of clinical studies, researchers (Semmes et al, 1960, Carlson et al, 1990) devised several studies wherein assortments of cortical lesions made in the Old World anthropoid macaque were correlated to deficits in a battery of tactile tasks. Major findings resulted, and these pointed to area 1 and area 2 as the cortical loci for processing of texture,

size and shape respectively. An ablation of primary somatosensory area 3b resulted in severe deficits on all tactile discrimination tasks.

Interestingly, another series of studies (Kruger & Porter, 1958) brought into play the possibility that the precentral gyrus might too have a functional role in somatic sensation. They again performed an assortment of cortical lesions that compared and contrasted the deficits observed after ablation of the postcentral gyrus alone, the precentral gyrus alone, or a unilateral ablation of both the pre- and postcentral gyrus. Combinatorial ablations with SII were also investigated. Ablation of area SI, or SI and SII resulted in an initial severe tactile defect in the contralateral limb but relearning of simple somesthetic form discrimination tasks occurred independent of whether the lesion was unilateral or bilateral. This was later reproduced in findings wherein SI lesions resulted in severe, long-term deficits in form and texture whereas an SII lesion alone caused little or no impairment. When SI and SII lesions were combined, no additional impairment was observed (Orbach et al. 1959). Ablations within M1 (Kruger & Porter, 1958) resulted in some temporary sensory defect but somesthetic form discrimination remained intact. In the event that a combined unilateral ablation of the pre- and postcentral arm area was made however, severe sensory loss in the contralateral arm was observed and the somesthetic discrimination task was no longer performed correctly. It is worth noting that these animals were able to discriminate object contour when the room was lit and they were able to make use of visual cues (Kruger & Porter, 1958).

These very interesting observations suggest that the primary motor area may play more of a role in somesthesis than is conventionally thought, and that these compensations may come into play after somatosensory cortical injury or deafferentation, but the supporting evidence has yet to be sufficiently resolved.

While some facets of the intricate somatosensory circuits remain murky, there has been substantial progress made and wide acceptance of how certain mechanisms vital to the processing of sensory information take place; we will focus on these. A concise review (see Darian-Smith, I. for extended review) of the somatosensory pathways most relevant to touch follows.

Somatosensation

The processing of sensory information is essential for maintaining arousal, controlling autonomic functions, controlling body movements, and for the conscious perception of sensation. We will primarily discuss the latter.

Our perceptions of the world around us are not indisputable properties of the world itself, but are our internal constructs of what we experience. These constructs are defined and constrained by the properties and capabilities of the nervous system. Early work by Weber (1846) and Fechner (1860) indicated that the nervous system constructed our sensory experiences via four basic characteristics of a sensory stimulus: its modality, location, intensity, and duration. The modality of a sensation refers to how different forms of energy are transformed by our nervous system into an experience of vision, taste, sound, or touch. Nerves within the body are primarily activated by one or another modality. Intensity relates to the strength of a stimulus, and the lowest stimulus intensity that a person can detect is the sensory threshold. It is worth noting that sensory thresholds are not absolute but can be altered by situational variables, among other things. The duration of a stimulus is important in sensory adaptation, a property partially coded for by sensory neuron excitability, and is critical for the detection of environmental change. The location of course indicates the site

of stimulation. Importantly, how good we are at indicating the site of stimulation actually depends on the site of stimulation, or more accurately, on the sensory nerve innervation that each part of the body receives. Specifically, in the tactile domain, the fingertips have a much greater density of receptor innervation than is found on the back. As such, we have considerably greater acuity at discriminating two spatially close stimuli on the fingertips vs. the back (where they may be felt as one stimulus). This is referred to as 'two point discrimination' (Kandel et al, 2000).

Most relevant to the topic at hand is the modality of touch, and the dependent variable under scrutiny is that of location. Specifically, the authors have sought to determine how the receptive fields within our somatosensory cortex that inform us of the source of a tactile stimulus and aid in two-point discrimination are affected after spinal cord injury. Findings will be discussed in a later chapter.

The Receptive Field

When one's skin is touched, the mechanical energy is detected by specialized sensory mechanoreceptors. Neural transduction and encoding then takes place via the electrochemical movement of ions across the sensory neuron membrane and an action potential is fired once a threshold has been crossed. This neural information is then carried to the cortex via second and third relay neurons. The underlying anatomy and pathways are illustrated later on. For the reason that each mechanoreceptor innervates a distinct portion of skin (with some overlap), specific location information is transmitted in a topographic manner along the pathways to the somatosensory cortex. From the moment then that activation of these receptive fields in the periphery leads to transduction within a circumscribed somatosensory territory in cortex, the conscious perception of a tactile

stimulus on a circumscribed part of the body is underway (Mountcastle, VB., 1980; Kandel et al, 2000).

As mentioned before, there is some overlap of receptor innervation in the skin. One might wonder why this is so for it may seem a costly strategy that impairs rather than assists in precise spatial localization of stimuli. Then again, can you imagine what dire consequences might result if the receptors in your developing nervous system 'missed a spot' and a portion of your skin was not innervated? More important however, are the advantages this sampling overlap conveys. Receptor neurons converge onto second-order neurons, with the receptive fields becoming progressively larger and more complex. Receptive field surround inhibition mediated by inhibitory interneurons then becomes critical for amplifying contrast and detection of the edges of a stimulus (Mountcastle, VB., 1980).

Anatomy of the Somatosensory System

Somatosensory information is relayed to the cortex via two primary ascending pathways: the dorsal column-medial lemniscal pathway and the anterolateral pathway. Peripheral nerves join together as they approach the spinal cord to form the spinal nerves, subsequent to which they enter the spinal cord via the dorsal roots. Once in the spinal cord, the majority of cutaneous nerves (along with proprioceptive nerves) ascend to the brainstem via the dorsal columns that lie medial to the dorsal horns. A small subset ascends via the spinothalamic tract of the anterolateral pathway. Whereas the lateral spinothalamic tract primarily carries pain and temperature information, the ventral spinothalamic tract transports information about crude touch as well. These axons arise from neurons in lamina 1 (pain) and in deep laminae of the dorsal horn. It is worth noting that collaterals of the large-diameter axons that

mediate touch information and proprioception also terminate in deep layers of the spinal cord's grey matter (Kandel et al, 2000; Darian-Smith I., 1984).

The Dorsal Column- Medial Lemniscal Pathway

The dorsal column pathway mainly consists of ascending afferent fibers and as many as 50% are axons of second-order neurons in the dorsal horn. These fasciculi of the upper and lower body remain somatotopically organized, eventually terminating in their respective cuneate and gracile nuclei in the brainstem. The fibers then decussate and ascend contralaterally within the medial lemniscus to the thalamus. There they synapse onto neurons in the ventral posterolateral nucleus. From the thalamus, projections ascend to the primary somatosensory cortex where they synapse upon excitatory pyramidal cells as well as interneurons (Darian-Smith I., 1984).

The Spinothalamic Tract

The spinothalamic tract is one of the three main pathways of the anterolateral system. Its primary function is to carry pain and temperature information to the brain, but it also relays information about crude touch and proprioception. Whereas the dorsal column-medial lemniscal pathway primarily originates from the collaterals of primary afferent fibers, the spinothalamic tract originates largely from second-order neurons within the dorsal horn. Over a few spinal segments, the tract decussates and cutaneous fibers ascend laterally to the dorsal column-medial lemniscal fibers before synapsing onto the ventral posterolateral nucleus of the thalamus. From there, they project to the primary somatosensory cortex (Darian-Smith I., 1984; Jones et al, 1982).

The perception of the shape, size or texture of an object (discriminative touch), as well as the sense of where the limbs are in space (proprioception) are mediated by the somatosensory cortex. Whereas proprioception is largely a function of the area 3a subdivision, discriminative touch is a function of the primary somatosensory cortex (area 3b), which sends projections to Brodmann's areas 1 and 2. Additional projections from area 3a and some sparse projections directly from the thalamus further enable these divisions to parse object properties such as size, shape and texture (Jones et al, 1982; Jones and Wise, 1977).

Processing of tactile information within the somatosensory cortex.

Within the dorsal column nuclei there exists a capacity for feed-forward and feedback inhibition. Feed-forward inhibition is the means via which one group of neurons can inhibit another group also receiving information from ascending primary afferents. Alternatively, recurrent inhibition occurs wherein relay nuclei synapse onto inhibitory interneurons that hyperpolarize competing neurons. This means that of competing incoming signals, there is an amplification of contrast and only the strongest will be transformed and relayed to cortex (Kandel et al, 2000).

As is the case for mechanoreceptors in the skin, neurons in the somatosensory cortex have specific receptive fields. As such, tactile stimulation to each point on the skin will activate a specific subset of neurons connected to those primary afferent fibers, and all will have similar receptive fields. Similarly, when a specific population of neurons in the somatosensory cortex is stimulated, a tactile sensation is felt on the skin. The cortical space dedicated to a particular region of the body is not left to chance however. For those areas where great tactile discrimination benefits the animal, greater innervation density is observed. As such, the number of receptors innervating a square centimeter of a fingertip greatly

exceeds the number innervating the same space on the back or trunk. Concordantly, the amount of cortical space dedicated to processing information from the fingertips exceeds that of the trunk, and the cortical receptive fields of the digits are much smaller than those of the trunk (Jones and Friedman, 1982).

One might wonder how it is that we are able to detect exactly where on our skin a stimulus is applied, or if there are two stimuli in close proximity, (without looking of course) given that there is such an overlap of receptive fields and that innervation density varies. This is better understood when we take a look at lateral inhibition.

When a tactile stimulus of sufficient threshold-crossing power is applied to the skin, the information is transferred via a responding population to each relay station of the neuraxis. At each station, (the dorsal columns for example), the cells for which the stimulus falls most within the excitatory regions of the receptive fields are those that are maximally excited. As such, they will also maximally excite inhibitory interneurons that synapse onto other competing neurons, effectively silencing the competition. This 'weaker' stimulus then is not relayed to cortex. In the event that two strong stimuli are applied to different points on the skin, separate cell populations will be activated, translated to cortex, and the inhibitory surround that separates each population will serve to amplify their peaks of activity and identify them as separate. Once in cortex, the columnar organization by submodality and the tendency for one modality to dominate within each of the body representations enables the separation and unique processing of object or tactile properties such as the texture of a stimulus, whether the indentation of skin is superficial or pressured, the size and the shape (Mountcastle and Darian-Smith, 1968).

Plasticity within the somatosensory cortex

The malleable nature of cortex has been evidenced in a vast number of studies in the past three decades, and along with it an effort to direct plasticity in a manner beneficial to those who have suffered damage to the central nervous system (CNS). Injury to the CNS may take place at different levels of the neuraxis but there is a disproportionate occurrence of spinal cord injury, often resulting in somatosensory and/or motor deficits. Several models have been devised in an attempt to study the cortical and subcortical changes that accompany spinal cord injury, one of which incorporates severing the dorsal columns.

A complete lesioning of the dorsal columns at a rostral enough level has been observed to deprive somatosensory cortex of most activating inputs from all but a narrow strip of skin of the anterior arm, and those from the face (there is some tactile information passed along the spinothalamic tract) (Kaas, 2005). Partial lesions of the dorsal columns or dorsal roots also deafferent the brainstem nuclei and have been shown to cause behavioral deficits that have been quantified with sensorimotor coordination tasks such as the beam walking test, and the reach-retrieval task. Overall success on these tasks has been correlated with the extent and placement of the lesions made, and a tight correspondence has been observed between digit use and somatotopic maps derived. In one study conducted by Darian-Smith and Ciferri (2006), the digit maps recorded showed re-emergence of the digits that macaque monkeys had regained function of, but a silent zone was observed for the digit not made use of again. In year 2000, Jain demonstrated a reorganized somatosensory area 3b in the owl monkey after an incomplete dorsal column lesion at C4/C5. Following multiunit electrophysiological recordings more than a year later, receptive fields for the face were observed in the hand and

arm region. Brainstem histology evidenced this as an extension of axon terminals from the trigeminal nucleus into the nearby cuneate nucleus (Jain, 2000).

Similarly, axonal sprouting was thought to play a role in the emersion of abnormally large cutaneous receptive fields in a considerably reorganized cortex in the macaque subsequent to spinal hemisection at segments C3/C4 (Darian-Smith, 1996).

What was common to both studies and several others involving dorsal column lesions was that the completely deafferented digits remained unresponsive and cortex normally allocated to these digits became invaded by nearby intact afferents. This new functional innervation was thought to underlie what behavioral improvement was observed. Completely deafferented digits did not regain dedicated cortex and corresponding silent zones were observed after recording, but receptive fields for digits that had only been partially deafferented were observed in ectopic and expanded cortical locations.

These studies ably depicted a concomitance of possible resulting changes in area 3b of cortex after varying interventions such as: denervation from the periphery such as via median nerve transection, and central lesions such as dorsal rootlet and dorsal column sectioning. Further weighty variations included differences in post-lesion survival time from weeks to years, and of course the species used.

In the next two chapters, we will discuss resulting changes in somatosensory cortex of two species of primates subsequent to lesioning of the dorsal columns.

There are two major subgroups of primates. These are categorized via fossil records, genetic comparisons, consideration of distinct cranial, dental, and skeletal morphologies, among other features. The prosimians (e.g. lemurs and lorises) are a grouping of mammals with characteristics considered more primitive than those of anthropoids. The generally larger

anthropoids (monkeys, apes, and humans) emerge from 2 lineages: the New World monkeys and the Old World monkeys. Old World monkeys are largely native to today's Africa and Asia, typically lack prehensile tails, and have downward facing noses (Catarrhines). They usually have more complex brains and are more closely related to humans. New World monkeys are largely native to Central and South America, and have side-facing nostrils (Platyrrhines). More often than not, they are arboreal and most have a prehensile tail that acts as a fifth limb.

The squirrel monkey (*Saimiri sciureus*) and common marmoset (*Callithrix jacchus*) are New World monkeys with notable differences not only in their skeletal morphology but also in the cortical representation of the forelimb. Whereas the normal squirrel monkey cortical area 3b depicts a tidy progression of the digits 5 to 1 mediolaterally in separable territories (Sur et al, 1982), the marmoset 3b hand representation is not as divisible (Krubitzer and Kaas, 1990). Concordantly, the marmoset shows less skilled hand usage and, with the exception of digit 1(D1), has claws rather than nails.

Marmosets are of especial interest when one goes about investigations into primate evolutionary changes because they defy easy categorization. As such, they are preferable candidates for capturing a 'freeze-frame' of evolutionary change, and for investigating exceptions to the 'common plan' of cortical organization. Marmosets are classified as New World monkeys of the Callitrichid family, and are primarily from Brazil and the edge of Bolivia. They are among the smallest species (100-750g), and are considered amongst the most primitive. Alike Old World monkeys, they have 32 teeth vs. 36 but this is thought to be an adaptation due to their small size. Although arboreal, they lack prehensile tails. Another unusual characteristic is that they are monogamous in captivity, and although they have a simple uterus and a single pair of nipples, they give birth to dizygotic twins that are often

taken care of by the males. Alike other New World monkeys, they have sideways-facing nostrils, and skeletons with relatively long trunks, tails, and legs. However, unlike other New World monkeys their thumbs are not at all opposable, and as mentioned above, they have claws vs. nails on four fingers. It has been suggested that they re-evolved claws to aid in arboreal locomotion, and to cling to the sides of large tree trunks to feed on their preferred diet of sap, gum, and insects (Fleagle, 1999). They primarily employ a power grip (opposition of digits to palm) but lack the dexterity of a precision grip (opposition of D1 to D2) (Krubitzer & Disbrow, 2006).

Most interesting to the topic at hand is their brain organization. Specifically, their sensory cortex has more features in common with that of the more primitive prosimian than with other anthropoids. This includes a cortex lacking in substantive folds (their brain is lissencephalic), and the lack of a central sulcus (Carlson 86).

Bearing in mind these differences, we have incorporated a marmoset model in our studies to see what, if any, impact these variations have on the resulting changes brought about after an injury to the primate posterior spinal cord.

Chondroitinase ABC digestion of the glial scar promotes neuroplasticity after injury

When multiunit electrophysiological recordings are carried out following peripheral deafferentation, neuronal receptive field shifts are shown to occur in only seconds. This form of plastic reorganization is thought to be due to the unmasking of horizontal connections via changes in the dynamic balance of excitation and inhibition, mostly due to less afferent-driven tonic inhibition (Nicolelis M., 1997).

The form of plasticity that takes place over a longer period of time is however, thought to result from the strengthening of weak synaptic connections and the formation of new

connections, e.g. from collateral sprouts. It is believed that these axonal sprouts form local synapses onto deprived postsynaptic neurons, thus amplifying the weakened signal from the periphery to thresholds detectable by the next processing station (Darian-Smith, 2006). For this reason, researchers have attempted to induce collateral sprouting from fibers that remain intact after injury, and one approach for doing so has been to administer the bacterial-derived enzyme chondroitinase ABC into the spinal cord lesion site or at the next synaptic station: the dorsal column nuclei.

The glial scar

A primary inhibitor of axonal regeneration subsequent to spinal cord injury is the glial scar that forms at the lesion site. When the blood-brain barrier has been compromised, connective tissue elements are able to invade the central nervous system. This intermingling of extraneous materials with astrocytic cells leads to an increase in the number of glia formed, i.e. reactive gliosis. The greater contribution to the glial scar however comes from astrocytic hypertrophy, wherein the glia become enlarged. This increased mass of enlarged and entangled glia is then observed to surround the dystrophic tips of axonal growth cones that become unable to extend their processes through the tangle (Miller and Silver, 2004). The inhibitory phenomenon of the glial scar is not without its benefits. Indeed, its function is to provide a barrier between injured and healthy tissue, thus stabilizing a fragile site within the CNS. The greater part of the resulting deficits that accompany CNS insult are usually not due to the primary site of injury but to the uncontained spread of leakage and excitotoxicity of those cells initially compromised to those in close proximity or synaptic contact. Thus, the glial scar walls off the damaged region, preserving intact tissue. The price for this protective

glial function is the greatly reduced ability of de-afferented fibers to reform long distance connections to denervated levels of the neuraxis.

The reactive gliosis that accompanies CNS insult brings with it an upregulation of proteoglycans. Proteoglycans are a class of glycoproteins that are found especially in the extracellular matrix of connective tissue. They are an essential component of the glial scar, and consist of a protein core linked by four sugar moieties to a sulfated glycosaminoglycan that contains repeating disaccharide units. (Johnson-Green et al, 1991).

One class of proteoglycans that has proven to be of interest in the study of axonal regeneration is the chondroitin sulphate proteoglycan (CSPG), whose expression increases following brain and spinal cord injury (Johnson-Green et al, 1991).

Several studies have indicated that this increase accompanies a reduction in neurite outgrowth. Snow et al (1992), for example, found selective retraction of axonal growth cone filopodia growing on alternating strips of growth- promoting laminin vs. CSPGs once the neurites came in contact with the CSPGs. They would however grow robustly on the laminin interface.

It is believed that it is the upset of equilibrium between growth - retarding and growth - promoting molecules within the astrocytic network following CNS injury that leads to the stagnation of axons at the lesion site. So it is then that researchers have thought to employ methods of reducing CSPG presence in the injured CNS to create an environment that induces dendritic outgrowth.

In support of these efforts, it has been shown that a reduction in inhibitory CSPGs in the immediate area of insult leads to an upsurge of collateral sprouting from axons that have survived the injury. These collateral sprouts seem to form functional connections leading to

a surge in afferent drive, thus amplifying a weak signal to a level detectable by target structures. For this reason, the attempt to induce collateral sprouting of partially denervated afferents via application of the CSPG-dissolving chondroitinase ABC remains ongoing. Chondroitinase ABC (chABC) is an enzyme derived from bacteria Proteus vulgaris. It serves to selectively remove part of the CSPG glycosaminoglycan (GAG) side chain, leaving only the protein core behind. It has been shown that as little as a single administration of 50U/ml protease-free chABC can prevent the rise in GAG concentration that occurs after CNS injury. Typically, such an increase peaks at 7 days, returning to normal by 28 days. Following treatment with chABC, enzymatic activity remains sufficient to digest newly synthesized CSPGs for at least 10 days post-infusion, sufficient time for permitting dendritic extension (Lin et al, 2008).

Chondroitinase ABC application in the spinal cord and brainstem nuclei.

The problem of forming new functional connections after spinal cord injury-induced disconnect has proven itself a difficult task for researchers. Most notable is the attempt to coax axons that have been cut to then extend their processes through the highly inhibitory oligodendroglial lesion site.

A variety of approaches have met with some success, and prominent among these is the use of degradative chondroitinase ABC to permit axons to cross the bridge into host tissue. Bradbury (2002) for example, after cervical dorsal column crush lesion, administered this enzyme intrathecally and observed promoted regeneration of both ascending sensory projections and descending corticospinal tract axons through the injury site. Similar observations have also been made following transections as described by Yack et al, (2002).

In these cases however, axons failed to grow more than a few millimeters outside the "restricted penumbra of the lesion site, and thus failed to influence distal regions of the nervous system" (Cafferty et al. 2007).

Collateral sprouts however, have been shown to form new functional connections onto deprived post-synaptic sensory neurons. Given the limitations of chABC to induce long distance sprouting but to nonetheless induce sprouting, efforts of some have been redirected toward application of chondroitinase ABC into the brainstem after spinal cord dorsal column section. The brainstem nuclei comprise the cuneate and gracile nuclei: the next synaptic station after dorsal horn entry of dorsal root ganglia in the dorsal column-medial lemniscal pathway. Perhaps then, increased sprouting and the formation of new synapses at the level of the brainstem nuclei where inhibitory molecular cues are not sufficiently upregulated to deter growth, would lead to amplifiation of the signal from the fibers remaining after injury onto postsynaptic neurons. It is with these expectations that Massey et al (2006) injected chondroitinase into the ipsilateral cuneate nucleus after spinal cord transections at a C6/C7 level that denervated digits four, five (D4, D5), and part of digit 3 (D3) of Sprague Dawley rats. Cholera toxin B-subunit (CTB) tracing immunoreactivity at the level of the cuneate nucleus subsequently indicated a sprouting of the remaining D1 and D2 afferents into the area that had been denervated.

We will shortly discuss the effects seen at the level of the cuneate nucleus and primate somatosensory cortical area 3b subsequent to intra-medullary application of chABC after spinal cord injury.

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