ORIGINAL CONTRIBUTION

Tracking Down CNS Reorganization: Future Sights and Sounds of Somatosensory Research

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Basic science research on somatosensory reorganization may reveal information on neural plasticity that is critical to preventing phantom limb pain. Somatosensory research in animals relies on techniques that differ considerably from the in vivo methods employed by neurologists. In the past, the majority of research in this area was conducted at one level of the central nervous system (CNS) with a single recording electrode. More recently, new techniques have been introduced into the field of somatosensory reorganization research.

A brief description has been made for the following techniques: single and multi-site electrophysiology, neural tracing, immunocytochemistry directed against the products of late and immediate early genes, as well as optical imaging. This paper reviews and evaluates these techniques for their contributions to understanding somatosensory reorganization and the underlying mechanisms of neural plasticity.

INTRODUCTION

Basic science investigations on neural plasticity provide the theoretical underpinnings for a wide range of applied and clinical investigations on central nervous system (CNS) function. Mechanisms of plasticity, for example long-term potentiation, have been implicated in the normal processes of learning and memory as well as a variety of neurological disorders [1, 2, 3, 4]. One long-term application of this research is to control the mechanisms of neural plasticity to promote healthy reorganization of the CNS following injury (i.e. spinal cord) or amputation.

Many amputees suffer from false or "phantom" sensations from the removed limb or breast [5, 6, 7, 8]. These sensations can be psychologically disturbing and painful and therefore significantly reduce quality of life. One hypothesis is that phantom sensations result from aberrant or inappropriate CNS reorganization following amputation and/or mastectomy [5].

Animal research on the reorganization of the somatosensory system in the adult mammal is expected to provide insights for new treatments to ameliorate or reverse phantom sensations. In the present paper we review past and future directions for research on the reorganization of the adult mammalian somatosensory system. An emphasis has been placed on evaluating the new technical directions for identifying neural plasticity within the CNS.

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The Somatosensory system

Whenever a piece of skin is touched a corresponding set of cells is activated in the CNS. Excitation is relayed transynaptically within the ascending somatosensory system until this information reaches the cerebral cortex. This system is characterized by a reliable spatial organization whereby adjacent patches of skin are represented by neighboring central neurons. This somatotopy is preserved throughout the ascending somatosensory system. It is this organization of projections that builds the homunculus, the distorted representation of a body stretched across the cortex common to most anatomy textbooks [9].

The original bio-electric signal is generated by distortions of the skin's mechanoreceptors that are embedded in the epidermal and dermal layers. Activity at these sensory nerve endings is sent to the spinal cord where it is projected to the dorsal column nuclei. Information from the upper body is relayed through the cuneate nucleus whereas the gracile nucleus represents information from the lower body. It is at these brainstem nuclei

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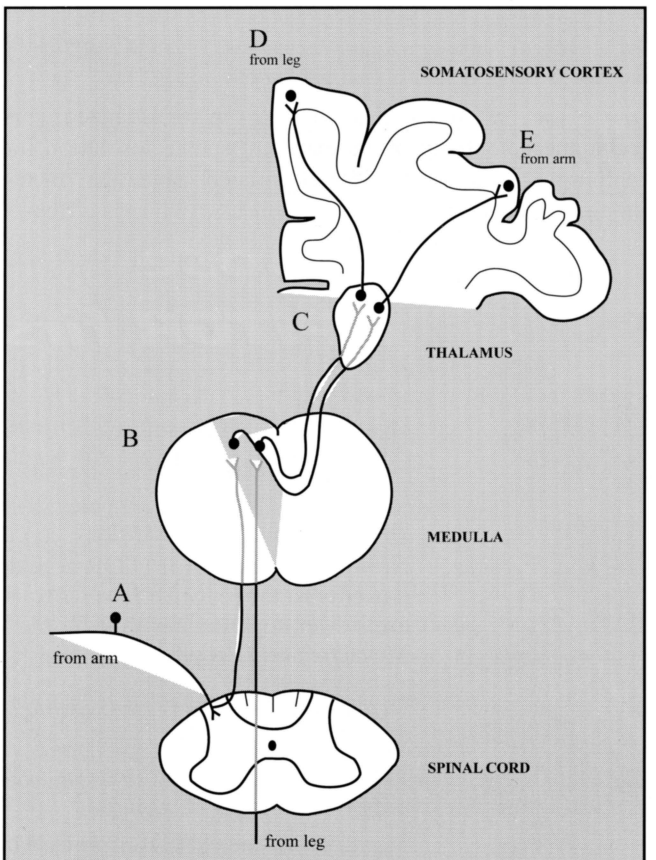

Figure 1

Dorsal column medial lemniscal system. Three levels where a somatotopic map can be found: Information travels into the spinal cord through the dorsal root (A) and then project to cells in the medulla. These cells are organized into two somatotopic maps. The map for the upper body is found in the cuneate nucleus whereas the lower body is represented in the gracile nucleus (B). These brainstem neurons project to the ventroposterior lateral nucleus of the thalamus (C) which in turn send their axons to the cortex (D and E).

that the signal "enters" the brain. These cells synapse with cells in the ventral posterior lateral nucleus of thalamus. The thalamic neurons, in turn, project to the cortex.

At this CNS level, the first and dominant sensory signal is received at the primary somatosensory cortex, however, considerable association cortex is also dedicated to processing sensory inputs from the skin [9].

The Reorganization Process

Studies of CNS reorganization are concerned with how communication between brain and skin is rearranged following the disruption of the original connection between a neuron and its receptive field. Once a neuron in the CNS has lost its primary afferent input, it will begin to acquire a new receptive field on the remaining portion of the receptive sheet [10, 11, 12]. These findings cannot be explained by the regrowth of peripheral neurons but rather, have been postulated to reflect changes in the connectivity within the CNS [13].

Monitoring CNS Reorganization

One of the most common, and oldest, experimental methods used to monitor CNS connectivity and re-connectivity is electrophysiology [14]. A great deal of progress has been made in mapping sensory pathways with single cell and multi-unit activity electrophysiological recordings. In this process bio-electrical events, for example action potentials, are amplified and recorded. When regions of the skin are stimulated, the corresponding area of the central nervous system becomes active. By pairing the skin stimulation with the activation of neurons it is possible to establish functional connectivity between the skin and the brain. Reorganization of the CNS can therefore be assessed by the altered functional connectivity that follows the loss of the original input.

There have been remarkable technological advances in the ability to monitor brain activity. Clinically, functional magnetic resonance imaging (fMRI) and positron emmision tomography (PET) scans are amongst the most popular tools [6]. Exciting new techniques are also gaining popularity in basic science. It is these new scientific directions that are the focus of the present article. The purpose of the remainder of this review is to describe and critique new technical directions in identifying neural plasticity generally, and how these mechanisms may be incorporated within the process of CNS reorganization.

Multi-Site Electrophysiology

Recently a new approach to electrophysiology has gained popularity within the field of CNS reorganization research. This technique employs "multiple ensemble recordings" that simultaneously register the activity of as many as 100 neurons per animal from different regions of the brain [15]. It has been possible to employ this technique in freely behaving animals over long periods (8 - 15 months in monkeys) [16]. One of the interesting findings made possible by using this technique is that the same tactile stimulus appears to be encoded almost simultaneously within three cortical areas [17].

Perhaps one of the most important applications of this technique is to follow more closely the afferent flow of information in reorganizing sensory systems. With this technique it would be possible to quantify the extent and time course of reorganization at all levels of the somatosensory pathway.

Despite excellent temporal resolution for neural activation, each electrode can only detect activity from a relatively narrow spatial field around each electrode and the number of electrodes that can be used in a given area without damaging neural networks is limited. There are other techniques, such as optical imaging, that are better suited to studying spatial patterns of neural activation. One advantage of electrode recordings over optical imaging is that it is possible to record from multiple levels or deep structures of the central nervous system. The most significant challenge in multi-site electrophysiology is understanding the temporal relationships of neural activation. Perhaps the most complicated chal-

lenge to overcome using this technique is appropriate data analysis. Temporal relationships in neural systems are highly complex. The reorganization process and the corresponding pressure to store the new functions within the deafferented zone further complicate the situation.

Neural Tracing Studies

Neuronal tract tracing is one of the most definitive methods for showing changes in anatomical connectivity after CNS reorganization. Neuronal tracers such as wheat germ agglutinin or fluororuby are injected into a region of interest. The tracer attaches to part of the cell and in many cases is internalized and transported throughout that cell. One of the most interesting ongoing debates in reorganizational research is the extent to which altered functional connectivity depends upon altered anatomical connectivity [18, 19]. It has been shown, however, that the tracer can potentially label any cell along the injection trajectory and therefore, this technique may be of limited value in assessing changes in connectivity in a small spatial field or from injections made at deep structures [20]. In addition, there are major technical challenges to quantifying collateral sprouting following deafferentation and the suitability of this technique in assessing reorganization has been questioned [21].

Immunocytochemistry

Immunocytochemistry uses antibodies that are targeted against epitopes of a protein of interest. A variety of chromogens have been developed to identify this type of complex so that the immunoreactive sites can be visualized. This technique potentially offers excellent spatial resolution for regions that undergo alteration during reorganization. In addition, immunocytochemistry can be used to differentiate baseline levels of a plasticity-related protein and assess the changes in their expression at different time-points during the reorganization process.

A wide variety of commercially available antibodies have been developed to identify proteins that can be associated with neuronal plasticity. For example, elevated growth association protein 43 (GAP-43, also known as neuromodulin and B-50) expression is strongly correlated with the remodeling and growth of the nervous system after regeneration [22, 23].

A second antibody used as an immunocytochemical marker for CNS plasticity is synapsin I. This vesicular phosphoprotein regulates neurite development as well as the maturation of synaptic contacts. A putative role of synapsin I in neuroplasticity is to increase calcium-induced neurotransmitter release. Increases in both GAP-43 and synapsin I have been demonstrated in cat visual thalamus. However, the effect was not robust and the period of elevated protein expression was short [24]. To date, these tools have not been used exten-

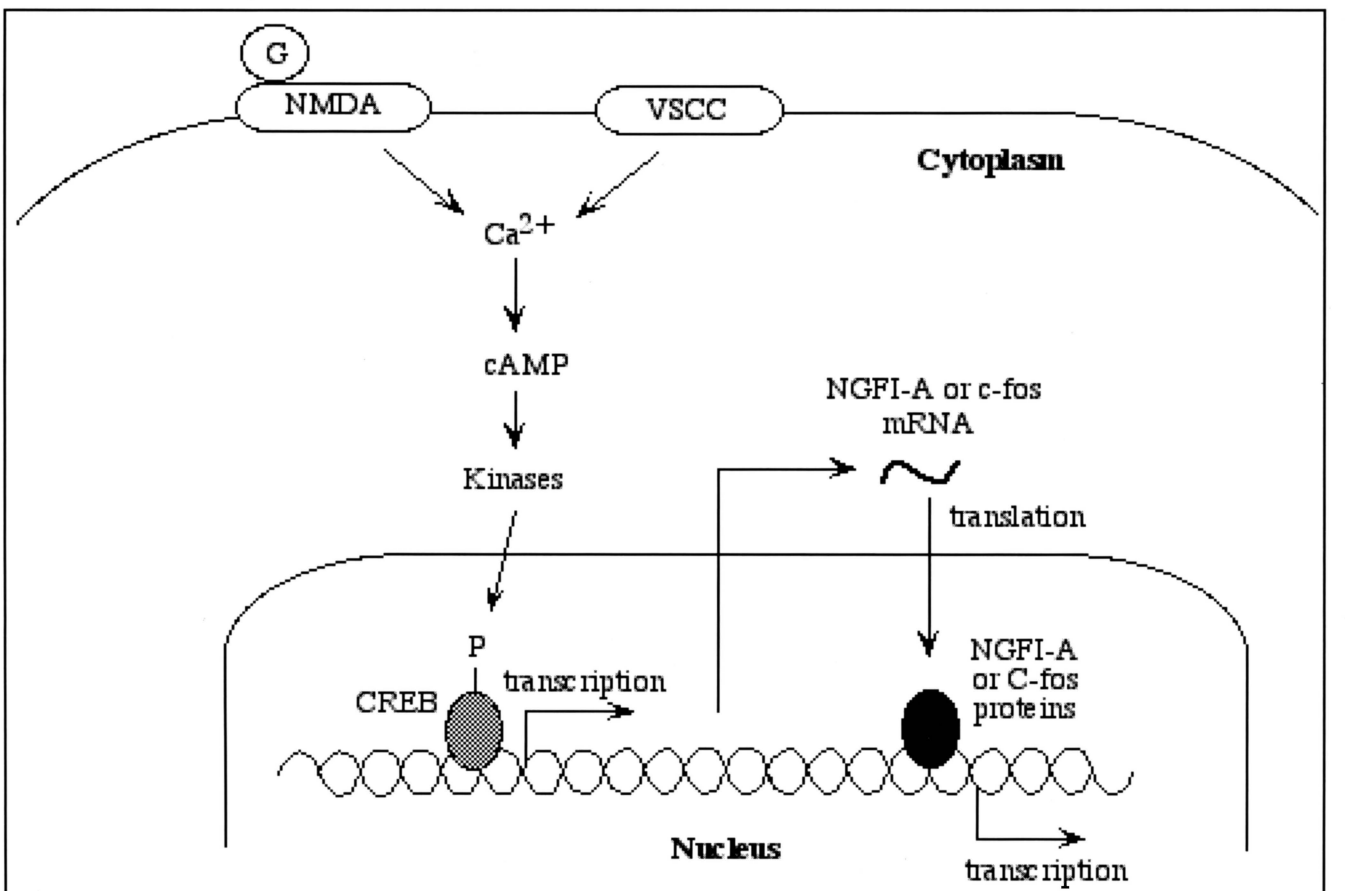

Figure 2. Schematic representation of the molecular pathways involved in the induction of the immediate early genes c-fos and NGFI-A. Abbreviations: G – glutamate, NMDA – N-methyl D-aspartate receptor, VSCC – voltage sensitive calcium channel, cAMP – cyclic adenosine monophosphate, CREB – cAMP responsive element binding protein.

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sively in reorganizational studies of the somatosensory system, however we anticipate their use in the near future.

Immediate early genes as mapping tools for neuronal activation

Immediate early genes (IEGs) are characterized by fast and transient induction after cell stimulation without the requirement of new protein synthesis for their transcription. Therefore, the transcription factors (TFs) required for their transcription are constitutively expressed.

In the last 10 years, the induction of IEGs, mainly c-fos and NGFI-A, have been utilized as a mapping tool for neuronal activation [25, 26, 27, 28]. The expression of these genes is intimately, however not exclusively, related to synaptic stimulation [29]. IEGs encode proteins that act as TFs for another class of genes known as late genes, which are thought to play a critical role in structural and functional changes of the cell.

IEGs are induced after a change in the membrane potential, which promotes a calcium influx in the cell. This influx triggers a cascade of intracellular events that leads to transcription of this class of genes (for example c-fos or NGFI-A) within minutes after stimulation. The rapid accumulation of specific mRNA in the cytoplasm serves as a template for the translation into protein products that accumulate in the nucleus.

Two techniques are commonly used to assess the products of IEG expression. In-situ hybridization, that is used to assess mRNA, consists of a probe (short *DNA or* RNA labeled strand) complementary to the transcriptional product of each gene that binds to the original mRNA of interest, which is synthesized as a result of gene expression. The result is the visual identification of the precise spatial locations of cells that are expressing the gene of interest.

In a second approach, immunocytochemical protocols are used to visualize the presence of the proteins encoded by this class of genes. One benefit of immu*nocyto*chemistry directed against the nuclear proteins NGFI-A or c-fos is that the immunopositive cells could be quantified. To the contrary, the quantification of in-situ hybridization can only be assessed in changes of the relative field expression profile.

Induction of IEGs in sensory systems and the relationship with plasticity

Several groups have analyzed variations in the levels of the products (mRNA by in-situ hybridization and protein by immunocytochemistry) of the expression of IEGs in a wide variety of stimulation conditions in several sensory systems [30, 31, 27, 32, 25, 26]. Within the somatosensory system, it was shown that tactile stimulation is capable of dramatically increasing the levels of several TFs in the rat brain [33].

It has been shown that the activation of the NMDA receptor is an important step in the elevation of NGFI-A levels, as well as in generating long-term potentiation (LTP). For these reasons, it has been postulated that NGFI-A may play a role in mediating plastic events that depend on the NMDA receptor [34]. Based on these findings, Wallace and colleagues [35] designed an experiment that showed that an enriched environment was capable of increasing NGFI-A levels in several areas of the rat brain. Interestingly, there was a strong spatial agreement between cortical areas where plasticity-related morphological changes have been identified, for example the somatosensory and visual cortices, and a relative increase in NGFI-A immunoreactivity.

Optical Imaging

Optical imaging can be performed with intrinsic signals of the cell or with the injection of calcium sensitive dyes. While both techniques are widely employed, it has been argued that the intrinsic signal is superior because it is non-invasive and does not require the introduction of a foreign substance to the cell [36]. This method of optical imaging exploits the reflective quality of biological tissue and its changes during different metabolic processes. These recordings reflect both spiking and sub-threshold activity and the technique has good spatial resolution over a wider area of the CNS.

In 1995, Das and Gilbert used optical imaging to show changes in cortical activation patterns due to reorganization in cat visual cortex [37]. The technique was useful in demonstrating that long-range horizontal connections play an important role in the reorganization of this system. One disadvantage of this technique is that changes in activity at deeper cortic*al la*yers cannot be detected.

Future Directions

There are two fields of technology that are highly likely to influence future neuroscience research. The first field is bionic neuron development. Biophysicists in this area build increasingly sophisticated artificial neurons that can be incorporated into biological circuits, in order to alter or study the performance of neural networks (Elson et al. – unpublished data).

The second field, nanobiology, is the convergence of applied nanotechnology biophysics, computer science and genetics. One of the most exciting developments within nanobiology is the use of proteins that can instruct the cell to change some aspect of its behavior. Researchers are exploring a variety of ways in which synthetic proteins could initiate intracellular repair or cell death in the case *of canc*er.

CONCLUSIONS

Within the field of electrophysiology, the convention of using single cell and multi-unit recordings has been expanded to include multi-site recordings. The impetus behind the development of this technique reflects a new theoretical emphasis on the behavior of neural networks.

The use of anatomical indicators of reorganization has shifted from neural tracing to immunocytochemistry and in-situ hybridization directed against the products of genes that are associated with neural plasticity. Of particular interest is the use of immediate early genes as indicators of change in

the relative levels of neuronal activation.

Historically, anatomical and electrophysiological data have been employed in a complementary way to characterize CNS reorganization. We expect this trend to continue, so that investigators will be correlating changes throughout the somatosensory pathway, for both functional and anatomical changes in activation patterns *due to plasticity.*

Two new avenues of research that are expected to yield exciting new approaches to understanding sensory systems are bionic neurons and nanobiology. The insertion of bionic neurons into neural networks is one way by which the behavior of the system could be manipulated experimentally, whereas nanobiology holds the promise *of exploiting the cell's* machinery to manipulate the entire process of reorganization.

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