

Symptoms and signs caused by neural plasticity

Aage R. Møller

University of Texas at Dallas, Callier Center for Communication Disorders, Dallas, TX, USA

Plastic changes in the central nervous system are associated with hyperactivity, hypersensitivity, and spread of activity including activation of brain regions that are not typically involved. Symptoms and signs such as neuropathic pain and tinnitus and hyperactive disorders such as muscle spasm and synkinesia may result from such changes in function. Plastic changes that cause symptoms of diseases can be initiated by novel stimulations, overstimulation, or deprivation of input and the induced changes in the function of central nervous system structures may persist and aggravate after these events have ceased if the condition is not reversed. Disorders that are caused by neural plasticity are potentially reversible with treatment. However, the absence of morphologic abnormalities makes diagnosis of these conditions difficult and their treatment has been hampered by lack of understanding of their pathophysiology. Here the role of neural plasticity in the pathophysiology of several disorders is reviewed. [Neurol Res 2001; 23: 565–572]

Keywords: Neural plasticity, neuropathic pain; muscle spasm; synkinesia; tinnitus

INTRODUCTION

It has been known for many years that the developing central nervous system (CNS) is plastic, causing its function to change in different ways as a result of external and internal factors. Only relatively recently has it become evident that the mature nervous system is also plastic^{1–15}. Neural plasticity is an ability of the nerve cells to change their function or structure. This is usually considered necessary for the developing organism, and beneficial to the mature organism because it can change the function of specific parts of the CNS to suit changing demands or compensate for the effect of injuries and diseases. It is neural plasticity that makes it possible for stroke victims to regain functions after destruction of neural tissue. Neural plasticity most likely also plays an important role in making it possible to adapt the nervous system to the use of prostheses such as cochlear implants and auditory brainstem implants. However, neural plasticity can also cause symptoms and signs of diseases. The symptoms that arise from functional changes that are expressions of neural plasticity are not associated with detectable morphologic or chemical abnormalities. This is in significant contrast to the symptoms and signs of disorders that are associated with tissue injuries and which usually can be identified by imaging techniques or by electrophysiologic methods.

Symptoms caused by neural plasticity have been studied most extensively with regard to pain^{4,15–24}, but neural plasticity can also cause other symptoms and signs about which less is known. The symptoms of neural plasticity may be hypersensitivity, hyperactivity and/or extended activation of central nervous system

structures including re-routing of information to regions of the brain that are not normally involved in a particular function. Allodynia, i.e. pain evoked by somatic stimulation that normally does not evoke pain, is an example of a symptom caused by changes in the CNS. Allodynia and phonophobia are signs of re-routing of information in the central nervous system evoked by sensory stimulation. Synkinesia is a sign of establishment of new connections between motoneurons. Other symptoms such as hyperalgesia (increased sensitivity to painful stimuli) and hyperpathia (exaggerated subjective response to painful stimuli that continue after the stimulation has ceased), and muscle spasm that may occur after peripheral nerve injuries, are signs of plastic changes resulting in hypersensitivity and hyperactivity. Tinnitus and certain forms of vertigo are examples of disorders that may be caused by plastic changes in the function of specific CNS structures resulting in hyperactivity or re-routing of information.

The plastic changes that occur in the mature nervous system are different from those that occur in the developing nervous system. The function of the developing nervous system normally changes during development and the abnormalities that occur are regarded as errors in the normal development. The mature nervous system is normally stable, except for changes that are related to aging. Altered excitability of specific neural structures, changes in synaptic efficacy or outgrowth of new connections (sprouting) are common changes attributed to neural plasticity. Expression of neural plasticity may occur as a result of external and internal events such as deprivation of sensory input, overstimulation, or tissue injury and inflammation. The same events may cause long lasting modifications or alterations in the expression of receptors¹⁹. Plastic changes in the nervous system may be regarded as a form of learning. Since plastic changes in function are not accompanied by tissue damage they are potentially reversible^{3,25–28}.

Correspondence and reprint requests to: Aage R. Møller, PhD, University of Texas at Dallas, Callier Center for Communication Disorders, 1966 Inwood Rd., Dallas, TX 75235-7298, USA. [amoller@utdallas.edu] Accepted for publication November 2000.

Most of the knowledge about expression of neural plasticity in the mature nervous system and how it can cause symptoms and signs of diseases has been gained from research on pain. The results from pain research have been used in attempts to understand how plastic changes may occur in other parts of the central nervous system and which symptoms and signs may result^{29,30}.

This review article provides an overview of the role of neural plasticity in causing symptoms and signs that result from changes in the function of the nervous system. Specifically, the role of neural plasticity in neuropathic pain, tinnitus, vestibular disorders, and synkinesis and muscle spasm is discussed.

SIGNS OF CENTRAL ORIGIN OF SYMPTOMS

Phantom sensations and phantom pain are perhaps the clearest demonstrations of disorders where the neural activity that causes the symptoms does not originate at the location of the symptoms^{26,28,31}. Phantom pain is therefore a pure form of central pain. Tinnitus that occurs despite a severed auditory nerve is also a clear sign of a central origin of the abnormal neural activity that causes the symptoms³⁰. It has been shown in animal experiments that the auditory^{1,2,8,12,13,32} and somatosensory sensory cortex^{3,7,15} may reorganize so that regions that are adjacent to the areas that are deprived of input expand to occupy the deprived cortical areas. Allodynia, where sensory stimulation that normally is innocuous is perceived as being painful, is an indication that abnormal connections have been established between the somatosensory nervous system and the pain circuitry^{4,16-18}. Some individuals with tinnitus after injuries to the auditory nerve perceive sounds from rubbing the skin, another example of abnormal connections between sensory systems³⁰. Synkinesis after peripheral nerve injuries²⁷ and in connection with hemifacial spasm³³⁻³⁶ is another example of a condition that is caused by establishment of new neural connections. The vertigo and nausea from head movements that is experienced by individuals with certain vestibular disorders³⁷ may also be caused by reorganization of the central nervous system.

Central neuropathic pain is often accompanied by depression¹⁶, which indicates that new connections between pain circuits and structures belonging to the limbic system have been established. Phonophobia, which often accompanies auditory disorders such as tinnitus, is a sign of abnormal connections between the auditory nervous system and structures belonging to the limbic system^{6,30,38}. Abnormal connections in the CNS can be established either by outgrowth of new connections (sprouting) or by increasing the efficacy of normally closed synapses (unmasking of ordinarily ineffective synapses). While outgrowth of new connections takes time, change in synaptic efficacy can occur without delay.

Plastic changes in the central nervous system often result in changes in processing of information. One sign of such change in information processing is altered temporal integration of painful stimuli in individuals with neuropathic pain³⁹.

NEURAL PLASTICITY RELATED TO SPECIFIC SYSTEMS

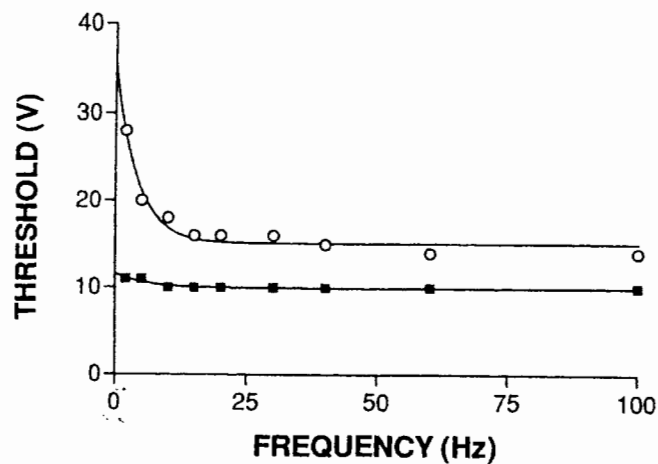
Somatosensory system

Paresthesia, hyperesthesia, neuropathic pain and pruritus are symptoms associated with disorders of the somatosensory nervous system. Disorders of the somatosensory system are also often associated with dysesthesia, i.e. an unpleasant sensation from stimulations that are normally innocuous. Some of these symptoms can be caused by peripheral neuropathies, hyperventilation or metabolic disturbances, but they can also be caused by plastic changes of the CNS. The symptoms that are caused by neural plasticity are not caused by neural activity that is generated at the location where the sensation is perceived, but rather by activity generated in the CNS. Allodynia and hyperalgesia are examples of symptoms that are caused by changes in the CNS. Pruritus (itching) is related to pain, and it can be caused by peripheral as well as central disturbances. Phantom limb sensations are examples of sensations that are generated in the CNS but referred to a peripheral location. The plastic changes that cause these symptoms may be induced by deprivation or over-stimulation. That phantom limb syndrome is related to over-stimulation is supported by the finding that avoiding over-stimulation during amputation by applying local anesthetics to the peripheral nerve can eliminate the occurrence of phantom limb sensations²⁸.

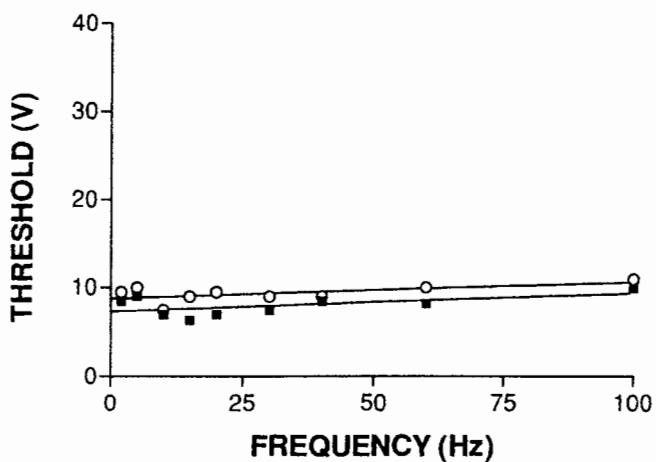
Pain

Neuropathic pain is an example of sensations that may be caused by neural activity generated in the CNS but referred to a peripheral location. Neuropathic pain can have many causes but the cause is less important for management than the mechanisms that produce the pain²¹. Woolf and Salter¹⁹ define three main types of pain: physiologic, inflammatory and neuropathic pain. Physiologic pain is caused by normal activation of nociceptors. Inflammatory pain is caused by various forms of inflammation and tissue damage. Neuropathic pain is caused by lesions of the nervous system, including lesions of peripheral nerves or disorders of the CNS such as strokes, but it is not known why lesions to the nervous system cause pain²¹. Neuropathic pain, or stimulus independent pain, may persist long after healing of the initial pathology and it is thus not a direct reaction to the pathology. Neuropathic pain may thus represent plastic changes in the function of the nervous system. Deafferentation pain (including *anesthesia dolorosa*) is an example of central pain. The regions of the body from where pain is referred often extend with time, thus a form of lateral spread of activation and a further sign of involvement of the CNS.

Sensitization of the CNS may cause the sensation of pain from stimulation of nociceptors to increase when the stimulation is repeated. This is known as the 'wind-up' phenomenon^{20,40}, and it is thus the opposite to adaptation in sensory systems. These changes are signs of central sensitization of excitatory synapses or by depression of inhibition¹⁹. Such plastic changes may be initiated by stimulation of nociceptors, by inflammation



A



B

Figure 1 A: Typical threshold curves for sensation (solid squares) and pain (open circles), shown as a function of stimulus repetition rate in two individuals without pain. The threshold functions for sensation and pain were fitted to exponential functions (solid lines). **B:** Typical threshold curves for sensation (solid squares) and pain (open circles), in an individual with neuropathic pain. (From Møller and Pinkerton, 1997)³⁹

or peripheral nerve injuries. Hyperpathia represents a modification of pain activation that may be caused by increased sensitivity of nociceptors caused by repeated stimulation (autosensitization), i.e., an exaggerated response to painful stimuli. Thus, more than transient activation of C-fiber nociceptors can induce central sensitization involving NMDA receptors^{41,42}.

Changes in temporal integration can be demonstrated by determining the threshold to pain from electrical stimulation with impulses presented at different frequencies³⁹. Normally, the pain threshold to stimulation with trains of impulses decreases when the interval between the impulses is decreased as an expression of temporal integration. The pain threshold is lowered in individuals with neuropathic pain and it does not decrease when the stimulus interval is decreased (Figure 1). Abnormal

temporal integration is a sign of involvement of the central nervous system in pain and testing of temporal integration could serve as a valuable diagnostic tool to differentiate between neuropathic pain of central origin and pain caused by stimulation of nociceptors (physiologic or inflammatory pain).

Recently, the administration of Botulinum toxin has been introduced for treatment of myofascial pain and other intractable headaches⁴³. Botulinum toxin that block muscle endplates is injected in muscles of the head. The efficacy of that treatment may be explained by neural plasticity that causes the output of proprioceptors to activate pain circuits, thus similar to 'allodynia' in neuropathic pain. The proprioceptors would be activated by muscle contractions. This may also be at least a partial explanation of other forms of pain from muscle spasm. The effect increased gradually over a 60-day observation period, which supports the hypothesis that neural plasticity of proprioception is involved. Naturally, muscle spasm may cause pain in muscles from exhaustion.

The abnormal connections between the somatosensory system and pain circuits in the spinal cord or brainstem that result in symptoms, such as allodynia, may be established either by unmasking of inefficient synapses⁴⁴ or by establishment of anatomically new connections through sprouting of axons^{4,22,45}. There is recent evidence that A-beta fibers may sprout from in the dorsal horn of the spinal cord into parts where C-fibers normally terminate^{4,22,45}. Such new connections between sensory fibers and neurons that normally receive input from nociceptors representing functional connections between the somatosensory system and pain circuits in the spinal cord may explain allodynia. Another possibility is a change in the function of the wide dynamic range (WDR) neurons in such a way that these neurons may increase their maximal firing rate to levels that can open normally inefficient synapses that connect these neurons to pain circuits¹⁷. Such changes may occur by reduction of inhibitory input to (WDR) neurons or by an increase in excitatory input to these neurons. The sympathetic nervous system may also be involved and produce a positive feedback of pain-evoked neural activity. The extreme expression of sympathetic involvement is reflex sympathetic dystrophy (RSD)⁴¹.

Establishment of new connections in the brain or spinal cord may also explain the affective components of pain. At least some of the affective attributes to pain may result from establishment of connections to the medial portion of the thalamus and to limbic structures. However, the pathways for nociceptive input (Figure 2)¹⁶, are complex and the pathways for neuropathic pain are likely to be even more complex with a high degree of parallel processing including connections with autonomic systems.

Tinnitus

Tinnitus is a common disorder of hearing that has many forms⁴⁶⁻⁴⁸. Most people who have tinnitus are

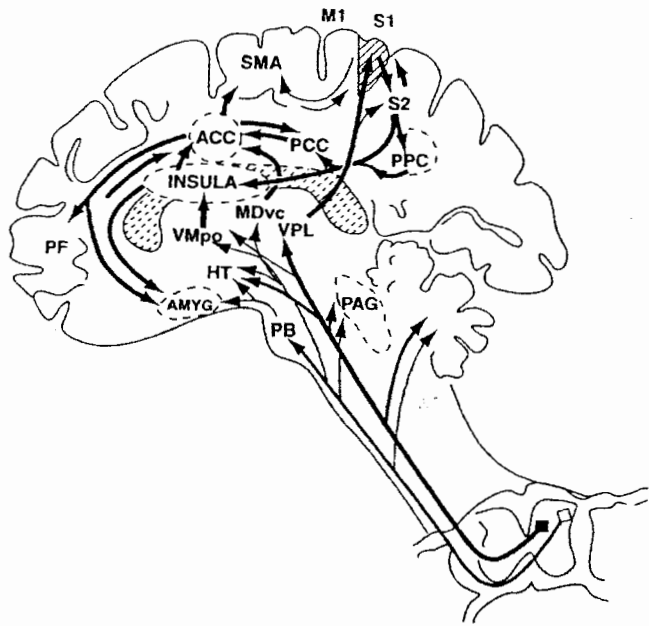


Figure 2: Schematic drawing of ascending subcortical and cerebral cortical structures involved in processing of pain. PAG, periaqueductal gray; PB, parabrachial nucleus of the dorsolateral pons; VMpo, ventromedial part of the posterior nuclear complex; MDvc, ventrocaudal part of the medial dorsal nucleus; VPL, ventroposterior lateral nucleus; ACC, anterior cingulate cortex; HT, hypothalamus; S-1 and S-2, first and second somatosensory cortical areas; PPC, posterior parietal complex; SMA, supplementary motor area; AMYG, amygdala; PF, prefrontal cortex. [Reprinted with permission from Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000; **288**: 176-1772. American Association for the Advancement of Science]

little bothered by their condition, but severe forms of tinnitus may affect the quality of life in a serious manner by preventing sleep and the ability to do intellectual work. Some forms of tinnitus are accompanied by hyperacusis and distortion of sounds. Phonophobia and depression with high risk of suicide may also be present in patients with severe tinnitus^{30,48,49}. Severe tinnitus has many similarities with neuropathic pain, both in the way it affects a person's life and in its pathology^{29,30}. However, tinnitus is rarely taken as serious as chronic severe pain, although it can be just as debilitating.

Since tinnitus is perceived as a sound it is often associated with disorders of the ear. The fact that deaf people can have tinnitus and that tinnitus may occur in individuals whose auditory nerve has been severed are strong indications that at least some forms of severe tinnitus are not generated in the ear. The hypothesis that tinnitus is a phantom sensation⁵⁰ that is caused by hypersensitivity and hyperactivity in specific central nervous system circuitry has been supported by many studies^{51,52}.

Tinnitus may appear gradually over many years of exposure to loud sounds, or it may appear after a single or a few instances of exposure to very loud sounds, especially impulsive noise. Tinnitus may also occur in

conjunction with acoustic tumors and other injuries or irritation of the auditory nerve such as from close contact with a blood vessel⁵³. Some individuals acquire tinnitus without any known cause. There is evidence that deprivation of input can cause temporary tinnitus and that permanent deprivation such as may occur in individuals with hearing loss can cause chronic tinnitus^{26,47}.

Sound deprivation can cause changes in processing of information in the auditory system in animals that resembles that seen in patients with severe tinnitus. Thus, Gerken *et al.*⁵⁴ found that deprivation of auditory input induces hypersensitivity of auditory nuclei and changes in temporal integration. Other animal experiments have shown that excessive stimulation of the auditory system can cause signs of hyperactivity and altered temporal integration in the inferior colliculus⁵². These changes were shown to be related to reduction in GABAergic inhibition^{52,55}.

The fact that many individuals with tinnitus perceive sounds as being distorted and find it difficult to match their tinnitus to physical sounds may be explained by a change in processing of auditory information. This hypothesis is supported by the finding that the non-classical ascending auditory pathways are activated in some individuals with severe forms of tinnitus, which does not occur in individuals who do not have tinnitus³⁸. This is a sign that neural activity has spread to other parts of the CNS beyond those normally activated by sound. The nonclassical auditory pathways project to the medial and dorsal portions of the thalamic relay (medial geniculate body) and the association cortices^{15,47}, which in turn have connections to the amygdala and other limbic structures. Activation of structures belonging to the limbic system can explain the emotional components of tinnitus. Activation of the nonclassical auditory pathway may thus explain why patients with severe tinnitus often have emotional reactions to sound (hyperacusis and phonophobia). Studies by Lockwood *et al.*⁶ using functional MRI in individuals who could control their tinnitus have confirmed that limbic structures such as the hippocampus are activated in some patients with tinnitus.

The nonclassical auditory pathways receive input from the somatosensory system, a fact that was used to show the involvement of the nonclassical pathway in patients with tinnitus³⁸. That may explain why some individuals can change their tinnitus by skin stimulation^{49,56,57}, or by contracting specific muscles⁵⁸. It may also explain why a few individuals have auditory sensations from skin stimulation. That some individuals can change their tinnitus voluntarily by changing their gaze⁵⁹, indicates that control of eye muscles modulates auditory pathways in some tinnitus patients. Such ability to modulate the intensity and the character of tinnitus seems to be most common in patients whose tinnitus is caused by surgically induced injuries to the auditory nerve, e.g. during removal of acoustic tumors, and it is further evidence of involvement of parts of the CNS other than those normally activated by sound, most likely the nonclassical auditory pathways.

Involvement of the nonclassical auditory pathway may also explain why tinnitus patients often find it difficult to match physical sounds to their tinnitus and when they find an acceptable match it is usually to sounds of very low intensity. This has been regarded as a contradiction to the severe discomfort these patients report and it can set a patient's description of his/her situation in doubt.

Vestibular disorders

Normally, we are not conscious of the activation of the vestibular inner ear apparatus. The nausea that results from head movements is a sign that information from the vestibular system has reached consciousness. Nausea and dizziness are not normal responses to activation of the vestibular system and must thus be caused by establishment of connections between the vestibular system and the conscious brain and the areas of the brain that cause vomiting. Disorders of the vestibular system, such as benign paroxysmal positional nystagmus (BPPN) characterized by nystagmus and dizziness from head movements, are most likely caused by an anomaly in the peripheral vestibular organ⁶⁰ that may send novel information to higher centers that cause a re-routing of information. Some of the abnormal sensations from head movement could be explained by malfunction of the vestibular system resulting in excessive muscle activity, which might be what the patient perceives. However, nausea and the feeling of dizziness seems to be a result of re-routing of information from the vestibular apparatus to regions of the CNS that usually do not receive such information.

Individuals with a rare disorder of the vestibular system, such as disabling positional vertigo (DPV)^{37,61}, experience nausea and discomfort from any head movement to an extent that it often forces such patients to spend most of their time in bed. This means that new connections from the vestibular system to brain regions not usually involved in processing information from the vestibular apparatus must have been established. The fact that these conditions may appear, and disappear, without noticeable delay indicates that these new connections are opened by functional changes (e.g. unmasking of ineffective synapses) that connect the vestibular system with regions of the conscious brain that are not normally activated by vestibular input. The fact that DPV can be successfully cured by MVD of the vestibular nerve root^{37,61} suggests that abnormal input from the vestibular nerve causes and maintains these abnormal connections (e.g. the abnormal neural activity may be caused by irritation of the vestibular nerve by a blood vessel (DPV) or as a result of malfunction of the vestibular organ (BPPN)).

Synkinesis and muscle spasm

Synkinesis and spasm are common sequelae of regeneration of injured peripheral motor nerves such as the facial nerve, indicating that abnormal connections have been established between motoneurons and the

target muscles. Post-traumatic synkinesis has often been interpreted as a failure of regenerating axons to reach their proper targets. This hypothesis has prevailed despite the lack of factual support. On the other hand, there is considerable evidence that plastic changes in the CNS can cause synkinesis and muscle spasm, by opening abnormal connections between motoneurons. This may occur, either by unmasking of inefficient synapses or by outgrowth of axons (sprouting).

Symptoms of spasticity and muscle spasm may be caused not only by hyperactivity of motor systems but also by altered proprioceptions. Thus, recent studies of facial motor control have shown evidence that post-traumatic synkinesis is a result of changes in the function of the facial motonucleus caused by injuries to the facial nerve⁶² and thus, is not a result of outgrowing axons having missed their target. This evidence combined with the evidence that facial exercise can reduce the synkinesis^{27,63} suggests that post-traumatic synkinesis is an expression of increased synaptic efficacy between motoneurons induced by injury to their axons.

Synkinesis often occurs together with muscle spasm in patients with hemifacial spasm (HFS)^{35,36}. HFS is a rare disorder⁶⁴ that is characterized by attacks of spasm in the muscles of one side of the face. It can be effectively cured by moving a blood vessel off the intracranial portion of the facial nerve, near its exit from the brainstem^{33,65}. The synkinesis can be demonstrated by testing the blink reflex^{36,66,67}, which can be elicited by electrical stimulation of the supraorbital branch of the trigeminal nerve. The blink reflex response is normally limited to the orbicularis oculi muscles but in patients with HFS it may also include contractions of other face muscles.

One of the two hypotheses about the cause of these signs postulates that the symptoms and signs of HFS are caused by crosstalk between axons at the location of the vascular contact with the intracranial portion of the facial nerve³⁴, while the other hypothesis claims that hyperactivity of the facial motonucleus causes these symptoms⁶⁸. Studies in patients undergoing MVD operations for HFS have supported the hypothesis that the signs of HFS (spasm and synkinesis) are caused by hyperactivity of the facial motonucleus^{36,67,69} and suggest that the synkinesis is a result of increased efficacy of synapses that connect facial motoneurons that innervate different muscle groups of the face^{36,69}. These synapses are assumed to be dormant under normal circumstances. The hyperactivity has similarities with the kindling phenomenon first described by Goddard⁷⁰ who showed that novel stimulation of a nucleus could lead to spontaneous activity. The novel stimulation that causes the facial motonucleus to become hyperactive may be generated by the irritation of the facial nerve from close contact with a blood vessel. This hypothesis was supported by studies of animal models of HFS^{1,5,11} in which similar signs, as in HFS (spasm and synkinesis), were created by electrical stimulation of the facial nerve according to a typical kindling paradigm^{5,10,11}. These studies thus indicate that the synkinesis in HFS is not a direct result of the close contact

between a blood vessel and the facial nerve but caused by abnormal connections between motoneurons, probably by the unmasking dormant synapses, which is initiated and maintained by the irritation of the facial nerve by a blood vessel.

If it is accepted that the function of sensory pathways may change as a result of neural plasticity, then it seems reasonable to assume that the processing of proprioceptive information can be modified or modulated. This means that abnormal motor function may not only be caused by abnormalities in the (descending) motor pathways but also by changes in proprioceptive feedback.

MECHANISMS OF NEURAL PLASTICITY

One of the first demonstrations of plastic changes in synaptic efficacy was made by Wall⁴⁴ who showed that deprivation of input can change the response areas of neurons. He showed that severing dorsal roots caused cells in the dorsal horn of the spinal cord to respond to input from dermatomes from which they normally did not respond. On the basis of these findings Wall⁴⁴ coined the term 'dormant synapses' to describe synaptic connections that exist anatomically but the function of which are blocked because they have high synaptic thresholds. Wall⁴⁴ explained how unmasking of such normally ineffective synapses can occur under abnormal conditions, such as deprivation of input. Synapses may be ineffective because the rate of the input is too low. Increasing the rate such as may occur as a result of novel neural activity can then open such synapses.

The unmasking of inefficient (dormant) synapses may extend sensory activation areas ('lateral spread') by opening connections to adjacent neurons. Such unmasking of dormant synapses can also open connections to regions of the brain that are not normally activated. Sprouting of axons may create anatomically new connections that have a similar effect of widening response areas. One of the earliest experimental demonstrations of that widening of the response areas as a result of changes (deprivation) of input was that of Merzenich and colleagues^{3,7} who showed that amputation of a finger causes the cortical representation of that skin area to be given to the adjacent fingers. Jenkins *et al.*³ showed that stimulation of the somatosensory system could also change the representation of body parts on the somatosensory cortex. These now classical experiments were followed by studies of other sensory systems where similar plasticity was demonstrated^{8,9,32} and showed that similar changes may occur because of other novel manipulations, such as overstimulation⁹.

Such 'lateral spread' of activation is a general sign of plastic changes and the widening of the response areas may be regarded as an 'un-sharpening' of response areas and motor projections, thus the opposite to what occurs in ontogeny where sensory receptive areas are narrowed by reduction in synaptic efficacy, pruning of axons and dendrites and apoptosis.

The phenomenon of 'lateral spread' may equally well be explained by sprouting of axons and dendrites to

form new connections. However, many of these changes occur with a very short delay, which preclude formation of new connections by sprouting. Morphologic changes have been shown to occur after overstimulation in the auditory system⁷¹⁻⁷³. Some studies indicate that outgrowth of new connections may be involved in chronic pain, where A-fibers in the spinal cord sprout from a location deep in the dorsal horn of the spinal cord into parts where C-fibers normally terminate and make synaptic contacts^{4,22,47}. This is assumed to be the cause of allodynia after peripheral nerve injuries.

If new connections are made by sprouting of axons, the effect takes some time to develop while unmasking of dormant synapses can occur instantly. In their original study of the establishment of new connections Wall and coworkers found that the new connections to dermatomes that they observed were made without delay. This means that it could not be a result of sprouting but could have been caused by an increase in synaptic strength. Wall and co-workers also showed that electrical estimation was more efficient in activating dorsal horn neurons from distant dermatomes than natural stimulations, which indicates that synapses may conduct when stimulated by high frequency stimulation while being unresponsive to low frequency stimulation. This means that pathways in the brain may become activated in response to novel input if the discharges have a shorter interval than the normal neural activity.

The fact that dizziness may develop suddenly excludes sprouting as a cause and indicates that the anomaly is the result of opening of dormant synapses in an already anatomically established pathway. Reversal of opening of ineffective connections may consequently be possible and there are examples of how training can alleviate some symptoms of such lateral spread. Thus, pain can be treated by TENS²⁵, tinnitus by the Tinnitus Retraining Therapy (TRT)⁵⁰, and synkinesis can be successfully treated by exercise as shown for the facial nerve²⁷.

Hyperactivity and hypersensitivity that may cause phantom sensations such as tinnitus, tingling and muscle spasm may be caused by strengthening of synaptic efficacy (long-term potentiation, LTP) or increased excitability of sensory receptors or centrally located neurons or by decreased inhibition. Studies of LTP in slices of hippocampus in rats or guinea pigs shows that it is best invoked by stimulation at a high rate. The effect may last from minutes to days and glutamate and the NMDA receptor (N-methyl-D-aspartate) have been implicated in LTP. Unmasking of ineffective synapses may occur because of increased synaptic efficacy or because of a decrease of inhibitory input that normally has blocked synaptic transmission^{1,2,8}.

CONCLUSION

The disorders that are caused by plastic changes in the function of CNS structures are characterized by distinct and prominent symptoms and signs but few objective signs, which complicates the diagnosis. The descriptions

of symptoms that patients present can be confusing because they often involve the events that were assumed to have precipitated the symptoms, e.g. trauma to a peripheral nerve, yet the symptoms of the patient often seem unrelated to these events. Lack of familiarity with neural plasticity as a cause of symptoms and signs may lead to erroneous diagnosis and ineffective treatment. The uncertainty about which medical specialty is best suited to care for patients with such disorders further hampers correct diagnosis and development of effective treatments.

The hypothesis that plastic changes in the nervous system may be the cause of symptoms and signs of certain disorders is attractive because it suggests that such disorders are potentially treatable, and understanding the cause of the plastic changes may make the disorders preventable. That the risk of acquiring some of these disorders can be reduced has been demonstrated. Yet the risk of many other disorders can probably also be reduced by appropriate intervention.

Many forms of chronic pain can be cured by electrical stimulation (TENS) but it requires proper diagnosis. Attempts to treat conditions that were initially triggered by peripheral events, which then progressed, by surgical intervention at the site of the pain is usually unsuccessful in alleviating the pain. This is most likely due to the resultant changes in the CNS. Equally unsuccessful are treatments of the ear in attempts to treat tinnitus that is caused by activity generated in the CNS.

The symptoms and signs that are discussed in this paper represent only a small fraction of the disorders that are caused by plastic changes in the central nervous system and many patients have received inadequate treatment because of failure to correctly diagnose their disorder.

REFERENCES

- Irvine DR, Rajan R. Injury- and use-related plasticity in the primary sensory cortex of adult mammals: Possible relationship to perceptual learning. *Clin Exper Pharmacol Physiol* 1996; **23**: 939–947
- Irvine DR, Rajan R. Injury-induced reorganization of frequency maps in adult auditory cortex: The role of unmasking of normally-inhibited inputs. *Acta Oto-Laryngologica* 1997; **532** (Suppl.): 39–45
- Jenkins WM, Merzenich MM, Ochs MT, Allard T, Guic-Robles E. Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. *J Neurophysiol* 1990; **63**: 82–104
- Kohama I, Ishikawa K, Kocsis JD. Synaptic reorganization in the substantia gelatinosa after peripheral nerve neuroma formation: Aberrant innervation of lamina II neurons by beta afferents. *J Neurosci* 2000; **20**: 1538–1549
- Kuroki A, Møller AR. Chronic vascular irritation of the facial nerve causes facial spasm in rats. *Neurol Res* 1994; **16**: 284–288
- Lockwood AH, Salvi RJ, Coad ML, Towsley ML, Wack DS, Murphy BW. The functional neuroanatomy of tinnitus. Evidence for limbic system links and neural plasticity. *Neurology* 1998; **50**: 114–120
- Merzenich MM, Kaas JH, Wall J, Nelson RJ, Sur M, Felleman D. Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. *Neuroscience* 1983; **8**: 3–55
- Rajan R, Irvine DR. Neuronal responses across cortical field A1 in plasticity induced by peripheral auditory organ damage. *Audiol Neurootol* 1998; **3**: 123–144
- Robertson D, Irvine DR. Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *J Comparative Neurol* 1989; **282**: 456–471
- Saito S, Møller AR. Chronic electrical stimulation of the facial nerve causes signs of facial nucleus hyperactivity. *Neurol Res* 1993; **15**: 225–231
- Sen CN, Møller AR. Signs of hemifacial spasm created by chronic periodic stimulation of the facial nerve in the rat. *Exp Neurol* 1987; **98**: 336–349
- Syka J, Popelar J. Noise impairment in the guinea pig. I. Changes in electrical evoked activity along the auditory pathway. *Hear Res* 1982; **8**: 263–272
- Syka J, Rybalko N, Popelar J. Enhancement of the auditory cortex evoked responses in awake guinea pigs after noise exposure. *Hear Res* 1994; **78**: 158–168
- Szczepaniak WS, Møller AR. Evidence of neuronal plasticity within the inferior colliculus after noise exposure. A study of evoked potentials in the rat. *Electroenceph Clin Neurophysiol* 1996; **100**: 158–164
- Wall JT, Kaas JH, Sur M, Nelson RJ, Felleman DJ, Merzenich MM. Functional reorganization in somatosensory cortical areas 3b and 1 of adult monkeys after median nerve repair: Possible relationships to sensory recovery in humans. *J Neurosci* 1986; **6**: 218–233
- Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000; **288**: 1769–1772
- Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution to central neuroplasticity to pathological pain: Review of clinical and experimental evidence. *Pain* 1993; **52**: 259–285
- Price DD, Long S, Huit C. Sensory testing of pathophysiological mechanisms of pain in patients with reflex sympathetic dystrophy. *Pain* 1992; **49**: 163–173
- Woolf CJ, Salter MW. Neuronal plasticity: Increasing the gain of pain. *Science* 2000; **288**: 1765–1768
- Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: Implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; **44**: 293–299
- Woolf CJ, Mannion RJ. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. *Lancet* 1999; **353**: 1959–1964
- Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992; **355**: 75–78
- Melzack R, Wall PD. Pain mechanisms: A new theory. *Science* 1965; **150**: 971–979
- Mendell LM. Modifiability of spinal synapses. *Physiol Rev* 1984; **64**: 260–324
- Willer JC. Relieving effect of TENS on painful muscle contraction produced by an impairment of reciprocal innervation: An electrophysiological analysis. *Pain* 1988; **32**: 271–274
- Jastreboff PJ. Tinnitus as a phantom perception: Theories and clinical implications. In: Vernon JA, Møller AR, eds. *Mechanisms of Tinnitus*, Boston: Allyn & Bacon, 1995: pp. 73–93
- Brach JS, VanSwearingen JM, Lenet J, Johnson PC. Facial neuromuscular retraining for oral synkinesis. *Plast Recon Surg* 1997; **99**: 1922–1931
- Bach S, Noreng MF, Thellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301
- Møller AR. Similarities between chronic pain and tinnitus. *Am J Otol* 1997; **18**: 577–585
- Møller AR. Similarities between severe tinnitus and chronic pain. *J Am Acad Audiology* 2000; **11**: 115–124
- Melzack R. Phantom limbs. *Scientific Am* 1992; **266**: 120–126
- Robertson D, Irvine DR. Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *J Comp Neurol* 1989; **282**: 456–471
- Gardner WJ, Sava GA. Hemifacial spasm – a reversible pathophysiological state. *J Neurosurg* 1962; **19**: 240–247
- Gardner WJ. Crosstalk – The paradoxical transmission of a nerve impulse. *Arch Neurol* 1966; **14**: 149–156
- Esteban A, Molina-Negro P. Primary hemifacial spasm: A neurophysiological study. *J Neurol, Neurosurg Psychiatry* 1986; **49**: 58–63
- Møller AR. Cranial nerve dysfunction syndromes: Pathophysiology of microvascular compression. In: Barrow DL, ed. *Neurosurgical*

- Topics Book 13, *Surgery of Cranial Nerves of the Posterior Fossa*, American Association of Neurological Surgeons: Park Ridge, IL, 1993: pp. 105–129
- 37 Møller MB, Møller AR, Jannetta PJ, Sekhar LN. Diagnosis and surgical treatment of disabling positional vertigo. *J Neurosurg* 1986; **64**: 21–28
- 38 Møller AR, Møller MB, Yokota M. Some forms of tinnitus may involve the extralemnic auditory pathway. *Laryngoscope* 1992; **102**: 1165–1171
- 39 Møller AR, Pinkerton T. Temporal integration of pain from electrical stimulation of the skin. *Neurol Res* 1997; **19**: 481–488
- 40 Thompson SWN, King AE, Woolf CJ. Activity-dependent changes in rat ventral horn neurons *in vitro*: Summation of prolonged afferent evoked post-synaptic depolarization produce a d-APV sensitive wind-up. *Eur J Neurosci* 1990; **2**: 638–649
- 41 Campbell JN, Raja SN, Meyer RA, Mackinnon SE. Myelinated afferents signal the hyperalgesia associated with nerve injury. *Pain* 1988; **32**: 89–94
- 42 Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiologica Scandinavica* 1997; **41**: 1124–1132
- 43 Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. *Pain* 2000; **85**: 101–105
- 44 Wall PD. The presence of ineffective synapses and circumstances which unmask them. *Phil Trans Roy Soc Lond* 1977; **278**: 361–372
- 45 Koerber HR, Mirnic K, Kavookjian AM, Light AR. Ultrastructural analysis of ectopic synaptic boutons arising from peripherally regenerated primary afferent fibers. *J Neurophysiol* 1999; **81**: 1636
- 46 Vernon JA, Møller AR, eds. *Mechanisms of Tinnitus*, Boston, MA: Allyn & Bacon, 1995
- 47 Møller AR. Tinnitus. In: Jackler RK, Brackmann D, eds. *Neurotology*, St. Louis, MO: Mosby Year Book, Inc., 1994: pp. 153–165
- 48 Møller AR. *Hearing: Its Physiology and Pathophysiology*, San Diego, CA: Academic Press, 2000
- 49 Møller AR. Pathophysiology of tinnitus. In: Vernon JA, Møller AR, eds. *Mechanisms of Tinnitus*, Boston, MA: Allyn & Bacon, 1995: pp. 207–217
- 50 Jastreboff PJ. Phantom auditory perception (tinnitus): Mechanisms of generation and perception. *Neurosci Res* 1990; **8**: 221–254
- 51 Gerken GM, Saunders SS, Paul RE. Hypersensitivity to electrical stimulation of auditory nuclei follows hearing loss in cats. *Hear Res* 1984; **13**: 249–260
- 52 Szczepaniak WS, Møller AR. Effects of (–)-baclofen, clonazepam, and diazepam on tone exposure-induced hyperexcitability of the inferior colliculus in the rat: Possible therapeutic implications for pharmacological management of tinnitus and hyperacusis. *Hear Res* 1996; **97**: 46–53
- 53 Møller MB, Møller AR, Jannetta PJ, Jho HD. Vascular decompression surgery for severe tinnitus: Selection criteria and results. *Laryngoscope* 1993; **103**: 421–427
- 54 Gerken GM, Solecki JM, Boettcher FA. Temporal integration of electrical stimulation of auditory nuclei in normal hearing and hearing-impaired cat. *Hear Res* 1991; **53**: 101–112
- 55 Szczepaniak WS, Møller AR. Evidence of decreased GABAergic influence on temporal integration in the inferior colliculus following acute noise exposure: A study of evoked potentials in the rat. *Neurosci Lett* 1995; **196**: 77–80
- 56 Cacace AT, Cousins JP, Parnes SM, McFarland DJ, Semenoff D, Holmes T, Davenport C, Stegbauer K, Lovely TJ. Cutaneous-evoked tinnitus. II. Review of neuroanatomical, physiological and functional imaging studies. *Audiol Neuro-Otol* 1999; **4**: 258–268
- 57 Cacace AT, Cousins JP, Parnes SM, Semenoff D, Holmes T, McFarland DJ, Davenport C, Stegbauer K, Lovely TJ. Cutaneous-evoked tinnitus. I. Phenomenology, psychophysics and functional imaging. *Audiol Neuro-Otol* 1999; **4**: 247–257
- 58 Levine RA. Somatic (craniocervical) tinnitus and the dorsal cochlear nucleus hypothesis. *Am J Otolaryngol* 1999; **20**: 351–362
- 59 Cacace AT, Lovely TJ, McFarland DJ, Parnes SM, Winter DF. Anomalous cross-modal plasticity following posterior fossa surgery: Some speculations on gaze-evoked tinnitus. *Hear Res* 1994; **81**: 22–32
- 60 Parnes LS, Price-Jones RG. Particle repositioning maneuver for benign paroxysmal positional vertigo. *Ann Otol Rhinol Laryngol* 1993; **102**: 325–331
- 61 Jannetta PJ, Møller MB, Møller AR. Disabling positional vertigo. *New Engl J Med* 1984; **310**: 1700–1705
- 62 Kreutzberg GW. *Neurobiology of Regeneration and Degeneration the Facial Nerve*, New York: Thieme, 1986: pp. 75–83
- 63 Johnson PC, Brown H, Kuzon WM, Balliet R, Garrison JL, Campbell J. Simultaneous quantitation of facial movements: The maximal static response assay of facial nerve function. *Ann Plast Surg* 1994; **32**: 171–179
- 64 Auger RG, Whisnant JP. Hemifacial spasm in Rochester and Olmsted County, Minnesota, 1960 to 1984. *Arch Neurol* 1990; **47**: 1233–1234
- 65 Barker FG, Jannetta PJ, Bissonette DJ, Shields PT, Larkins MV. Microvascular decompression for hemifacial spasm. *J Neurosurg* 1995; **82**: 201–210
- 66 Nielsen VK. Pathophysiology of hemifacial spasm: II. Lateral spread of the supraorbital nerve reflex. *Neurology* 1984; **34**: 427–431
- 67 Møller AR, Jannetta PJ. Blink reflex in patients with hemifacial spasm: Observations during microvascular decompression operations. *J Neurol Sci* 1986; **72**: 171–182
- 68 Ferguson JH. Hemifacial spasm and the facial nucleus. *Ann Neurol* 1978; **4**: 97–103
- 69 Møller AR, Jannetta PJ. On the origin of synkinesis in hemifacial spasm: Results of intracranial recordings. *J Neurosurg* 1984; **61**: 569–576
- 70 Goddard GV. Amygdaloid stimulation and learning in the rat. *J Comp Physiol Psychol* 1964; **58**: 23–30
- 71 Morest DK, Ard MD, Yurgelun-Todd D. Degeneration in the central auditory pathways after acoustic deprivation or over-stimulation in the cat. *Anat Rec* 1979; **193**: 750
- 72 Morest DK, Bohne BA. Noise-induced degeneration in the brain and representation of inner and outer hair cells. *Hear Res* 1983; **9**: 145–152
- 73 Willott JF, Lu SM. Noise-induced hearing loss can alter neural coding and increase excitability in the central nervous system. *Science* 1981; **16**: 1331–1332