Neurosensitization: A model for persistent disability in chronic pain, depression, and posttraumatic stress disorder following injury

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A neurosensitization syndrome (NSS) is defined as: a syndrome of subjective discomfort and objective functional disability; that often appears excessive in duration and severity with respect to the identified initiating injury or event; that may be resistant to conventional medical and psychological treatment modalities; and that is hypothesized to develop as the result of progressively enhanced sensitivity or reactivity of central nervous system (CNS) mechanisms at the neurophysiological, biochemical, and intracellular levels. This paper applies the neurosensitization model to the three syndromes which are frequently comorbid and treatment-refractory in clinical practice: (1) chronic pain; (2) depression; and (3) posttraumatic stress disorder. The understanding of how pathological behavioral syndromes spiral out of control may lead to productive, integrative medical, behavioral, and psychotherapeutic treatment strategies.

Keywords: Neurosensitization Syndromes (NSS), Traumatic Disability Syndromes (TDS), chronic pain, Posttraumatic Stress Disorder (PTSD), depression

1. Introduction

Many of the syndromes we see in mental health and rehabilitation settings reflect problems in adaptation and coping with injury of some kind, including postconcussive syndrome, chronic pain, posttraumatic stress disorder, multiple chemical sensitivity, and depression. Indeed, inasmuch as many injuries occur under frightening circumstances and may produce long-term disability that is demoralizing, many of these traumatic disability syndromes (TDS) [32] are frequently comorbid, creating vicious cycles of impairment and reduced quality of life.

These syndromes may also share common pathophysiological mechanisms that are important to understand from both theoretical and practical clinical perspectives. Indeed, current research pertaining to neuroplasticity and the effects of injury on the central nervous system has become one of the most active neuroscience fields to date [19]. Accordingly, the present paper will attempt to tie together some of the recent empirical and theoretical work in the area of traumatic disability syndromes, with specific reference to the commonly comorbid syndromes of chronic pain, depression, and posttraumatic stress disorder (PTSD), to develop a broader model of what I have called neurosensitization syndromes (NSS) [31]. A NSS may be defined as: (1) a syndrome of subjective discomfort and objective functional disability; (2) that often appears excessive in duration and severity with respect to the identified initiating injury or event; (3) that may be resistant to conventional medical and psychological treatment modalities; and (4) that is hypothesized to develop as the result of progressively enhanced sensitivity or reactivity of central nervous system (CNS) mechanisms at the neurophysiological, biochemical, and intracellular levels.

2. Depression

For most patients, the entry point into the mental health system is some variation of persistent dysphoric affect, and disorders of mood pervade and modify the clinical expression of most forms of TDS. It is a common clinical observation that mood disorders tend to occur in cycles, most obviously in the case of bipolar disorder, but also in the case of unipolar depression. The disorders may wax and wane along with circumstances in the life of the traumatically disabled individual, but often a depressive episode seems to occur in the absence of any identifiable precipitant, in which case the depression is termed “endogenous.”
To explain these cycles of affective disorder, Post et al. [44] have appealed to the paradigm of neurophysiological kindling, after the analogy with flammable material that must be heated to a certain critical temperature before ignition and self-sustained combustion occurs. First described experimentally with rats, kindling follows the repeated application of a stimulus, typically an electrical pulse, to the brain. Each individual application of the stimulus is insufficient by itself to evoke convulsive activity, but combined over an optimal sequential time pattern, the separate subthreshold stimuli summate to produce a seizure [1,17,47].

The brain structure most susceptible to kindling is the amygdala, a limbic system structure situated bilaterally in the anterior portion of the temporal lobe. Certain drugs administered to the brain can produce a progressive, kindling-like increase in neural excitability, so that the final dose – too small in itself to produce a seizure – will precipitate convulsive activity: the biochemical “straw that breaks the camel’s back.” The kindling model of drug action has been used to explain some cases of cocaine psychosis and other other human addictive phenomena [43,46].

It is the intermittency of the input that appears to be the critical factor in seizures kindled by amygdala stimulation [17,40,47]. Continuous stimulation or stimulation at relatively short intervals, e.g. minutes, does not result in kindling; rather, the animal habituates to the stimuli and no seizures are produced. However, if the intervals are extended to hours or days, habituation or tolerance does not occur; instead, there occurs a sensitization response, and such subthreshold stimuli eventually summate to produce a full-blown seizure.

Post [40,45] has used the kindling model to explain episodes of affective disorder that occur in response to intermittent stressful stimulation. For example, severe depressive states that appear to arise abruptly following a series of apparently successful coping attempts may reflect the summation of depressogenic influences on mood-mediating brain mechanisms occurring over a critical period of time. Any one or several of these challenges might have been handled adequately had they occurred individually or in a different temporal pattern. But many such stressors, occurring repeatedly over certain critical intervals of time, may summate to produce a full-blown kindled depressive disorder.

Kindling appears to represent a relatively permanent change in neural excitability; rats kindled in their youth retain heightened excitability into adulthood [1, 41,44]. After many repetitions of kindled seizures, an animal may exhibit what is termed spontaneity. That is, seizures or subconvulsive behavioral changes can now develop in the absence of any external stimulation, and about one-third of kindled animals show such spontaneous cycling in their seizure patterns [41]. Post et al. [45] suggest that the kindling model might explain how stress-induced mood alterations become sufficiently sensitized to occur spontaneously, providing one possible model for recurrent bipolar affective disorder.

Post [42] has focused on the microneuronal mechanisms that account for the kindled sensitization effect on experience and behavior. According to this expanded model, activation of neurotransmitter pathways produces not only acute events associated with rapid alternations in neural firing and short-term neural adaptation, but also much longer-lasting intracellular changes at the level of genetic transcription. One such change is the induction of a series of transcription factors, such as the proto-oncogene c-fos, that subsequently alter gene expression by binding at DNA sites and inducing messenger RNAs (mRNAs) for other substances that may exert effects over long time periods, i.e. days to months. Transcription factors, such as c-fos, by virtue of their acute (minutes to hours) effects, may provide the basis for a biochemical cascade of events that results in more enduring neurotransmitter, receptor, and peptide changes. These might provide the biochemical and anatomical basis for long-term synaptic adaptation and memory that could last indefinitely.

The oncogene milieu conditioned by prior experience may markedly affect subsequent alterations in gene transcription, so that the specificity and selectivity of responsiveness could be precisely regulated according to the number, intensity, and even the psychological meaning of prior experiences, and Post [42, 45] uses the kindling model to conceptualize how symbolic, or psychodynamic, influences can affect the biological bases of mental disorder. The sensitization-conditioning pattern of kindling suggests that the symbolic aspects of previous events that have set off a depressive response might be learned or conditioned so that they later come to elicit the depression even in the absence of the original stress or loss. Stressors related to separation, loss, and devalued self-esteem that are associated with the onset of depressive episodes following traumatic disability may play an important pathophysiological role in triggering repeated depressive episodes with each successive failure, frustration, or disappointment. The neurobiological encoding of memory-like functions related to these stressors may thereby induce progressively heightened long-term vul-
nerability to subsequent recurrences, and the retriggering of episodes with progressively lesser and lesser degrees of psychosocial stress. Ultimately, even anticipated stresses or imagined losses, as much as real ones, may be capable of producing the behavioral, physiological, and biochemical alterations of a full-blown depressive disorder, with its resulting cycle of isolation and repair.

3. Chronic pain

A common diagnostic association occurs between depression and chronic pain [5,14,21,22,28,29,33]. In many cases, no “legitimate” medical explanation for the pain can be discovered and patients make the rounds from clinician to clinician until they are eventually shunted into the mental health system. It may therefore be asked if some forms of chronic pain syndrome represent a species of neurosensitization syndrome.

In many cases, the chronic pain syndrome has a characteristic evolution and course [18,35]. The problem typically begins with some accident or injury which causes an expectable degree of acute pain requiring medical treatment. In a certain proportion of these patients, the pain and disability never seem to get better, and in fact, are reported by the patient to worsen with time. Various medical strategies are tried by the treatment team, but nothing seems to work. Excessive physical disability related to sleep and appetite disturbance complicate the picture, and are often exacerbated by the side-effects of excessive medication.

The patient’s ongoing struggle with continual pain frequently results in depression, obsessive somatic preoccupation, hypochondriacal concerns, death anxiety, and a tendency to increasingly conceptualize most life events, activities, and problems solely in terms of greater or lesser degrees of pain. This leads to a vicious cycle of hopelessness, helplessness, and despair. Each new treatment or physician briefly raises hope, which is followed by disappointment when the procedure fails to “cure” the pain. Resentment and bitterness grow toward the medical profession and this antipathy is often reciprocated, as doctors come to dread visits by the “crock.”

Pain now becomes the central focus of the patient’s life. External attachments and interests are abandoned, resulting in the patient’s withdrawal from family and social activities. Interactions are fraught with tension and anger. Problems with medication and with alcohol and drug abuse may compound the problem by producing toxicity and addiction. Pain behavior becomes a major coping mechanism, progressively allowing the patient to avoid any kind of stressful task or issue. This leads to further incapacitation, which aggravates the problem, alienates friends and family, and leads to the further decline toward total invalidism.

How patients think about and conceptualize their pain and its implications for their future may be an important factor influencing response to treatment and long-term outcome. Cognitive distortion is a factor that can have important emotional and behavioral effects [20]. Chronic low back pain patients are prone to “cognitive errors,” such as catastrophizing, overgeneralization, personalization, and selective abstraction. Patients who report engaging in high levels of cognitive distortion are found to be much more depressed than patients who do not [23].

Catastrophizing and overgeneralizing are related to excessive impairment in low back pain patients, especially with regard to sleep disturbance and impaired social relationships. Similarly, in rheumatoid arthritis patients, cognitive distortion has been found to be associated with increased depression and physical disability, even when controlling for disease severity [51,52]. The overwhelming majority of chronic pain patients may overestimate their baseline pain when asked to recall it following treatment [24], and subjects’ recall of the reactive and emotional quality of their pain appears to be particularly subject to distortion [25,48].

As noted above, the commonest diagnostic association of chronic pain is with depression [5,14,21,22]. Depending on the subject series, between 10 and 100 percent of chronic pain patients report depression [6,39]. According to the now-classic biogenic amine theory of affective disorders, depression reflects a disturbance in the catecholamine and serotonin neurotransmitter systems of the brain [49,50]. More recently, dysregulation of other transmitter systems, including brain enkephalins, have been added to the list [7,55]. A key argument for the biogenic amine theory of pain and depression is that antidepressant medications, which are known to increase the presynaptic availability of catecholamines and serotonin, are effective in alleviating both depression and pain. However, antidepressants do not relieve all pain states – or, for that matter, all depressions – and so the pain-depression link is unlikely to rest on any simple biochemical association [54].

A summary of what is currently understood about central nervous system (CNS) pain pathways includes the following: (1) the processing of nociceptive infor-
mation and pain is not exclusively related to a unique pathway, relay nucleus, or area in the CNS: (2) the simplest somatic sensory stimulus, nociceptive or innocuous, activates most (if not all) of the somatic sensory pathways, leading to a wide range of possibilities of interactions at spinal, brainstem, diencephalic, and cerebral cortical levels, and of feedback and feedforward modulatory loops, before ultimate integration that results in conscious perception; (3) this kind of complex balance existing between several systems and pathways carrying somatic sensory (including nociceptive) information could account for the multidimensionality of pain and the variability in the success encountered in all forms of pain treatment [19].

Coderre et al. [10] have proposed a central neuroplasticity model of chronic pain that appears to meet the present criteria for a neurosensitization syndrome. These authors review the data suggesting that peripheral injury can produce CNS changes which are maintained even after input from the injury is removed. Prolonged sensory disturbances associated with tissue injury are believed to result from either a reduction in the threshold of pain receptors or an increase in the excitability of CNS neurons involved in pain transmission. Sensitization within the CNS contributes significantly to this phenomenon. For example, repeated C-fiber afferent stimulation sequentially increases dorsal horn neuronal activity, resulting in a prolonged discharge of the neuron which lasts from seconds to minutes post-stimulation. This phenomenon, originally termed “wind-up” [27], sounds quite close to the mechanism of kindling described above and, according to Coderre et al. [10], could potentially occur following intense noxious stimulation or injury.

The physiology of behaviorally mediated pain responses has been reviewed by Flor et al. [15]. Pain episodes, as well as other stressors, may trigger a number of autonomic and musculoskeletal reactions, most notably sympathetic activation and elevated muscle tension. If stress or pain-related muscular contractions occur repeatedly or are sustained, mechanoreceptors will be activated, and this information is transmitted to the spinal cord. If stimulation exceeds a critical level, efferent fibers, such as the gamma motoneurons, may be activated, as well as sympathetic fibers that are connected with the smooth muscle of the blood vessels. These muscular and sympathetic reflexes lead to increases in muscle tension via the gamma motoneuron system, and to sympathetically mediated vasoconstriction.

Indeed, dysregulation of the gamma motoneuron circuitry has recently been proposed by Donaldson et al. [11] to explain the development of trigger point activity in myofascial pain syndrome. In this model, dysregulation in the gamma motoneuron circuitry may lead to disinhibition of muscle that causes it to remain hyperactive after contraction, generate excessive electrical activity during movement, and/or inappropriately coactivate with other muscles during movement. Such dysregulation may be corrected by learning, which has clinical implications for the evolution of pain behaviors.

If muscular contractions are of sufficient intensity, frequency, and duration, ischemia and hypoxia may develop in the affected muscle and lead to the release of pain-producing substances such as bradykinin. Subsequently, chemoreceptive pain receptors will be activated directly and the thresholds of mechanosensitive receptors will be lowered. The ensuing pain experience increases muscle hyperactivity and sympathetic activity, thus exacerbating the vicious cycle of chronic pain. Moreover, pain receptor input may be enhanced through sympathetic “overflow,” and extended stimulation of the sympathetic nervous system will lead to the release of adrenaline and noradrenaline, further increasing chemoreceptor sensitivity. Longstanding muscular contractions may lead to destruction of muscle fibers, chronic hypoxia, and depletion of intracellular ATP and phosphocreatine.

Further considering the role of peripheral mechanisms, the inflammatory cascade resulting from a trauma can lead to a silent cross-talk between the immune system and nervous system and to a vicious cycle established between neurogenic and tissue inflammations. Short-lived or long-lasting inflammatory processes can lead to changes in the function, and ultimately the structure of peripheral afferents that can trigger a cascade of functional and possibly structural changes at all levels in the CNS. In addition, inflammatory mediators and other factors can act directly on peripheral and central neurons leading to changes in the function of the hypothalamic-pituitary axis, which in turn lead to the behavioral and psychological changes characteristic of chronic pain – the peripheral and central mechanisms have come full circle [12,19].

Most of the data reviewed by Coderre et al. [10] support a neurosensitization model of chronic pain. Reports of pain in phantom limbs appear to be less common when there has been a pain-free interval between the painful experience and the amputation. Conversely, if pain is experienced at or near the time of amputation, there is a higher probability that it will persist in the phantom. Pain also persists in patients with deaf-
ferentation that does not involve amputation, such as brachial plexus avulsions and spinal cord injuries. In a number of cases, reactivation of the “pain memory” occurs in response to a peripheral trigger, sometimes months or years after the original injury. This suggests that certain brain mechanisms store these pain memories for long periods.

Neurons in the somatosensory thalamus of patients with neuropathic pain display high spontaneous firing rates, abnormal bursts of electrical activity, and evoked responses to stimulation of body areas that normally do not activate these neurons. The site of abnormality in thalamic function appears to be somatotopically related to the painful region. The cingulum bundle and fornix are part of a neural loop that projects from the anterior thalamic nuclei to the cingulate cortex, hippocampus, and mammillary bodies, and returns to the anterior thalamic nuclei. Coderre et al. [10] propose that activation of this closed neural circuit during the initial exposure to painful stimulation induces a sensitized state within the limbic system, enhancing responses to subsequent stimuli.

Conversely, clinical evidence suggests that administration of analgesic agents prior to surgery may prevent the central sensitizing effects of surgical procedures. In this manner, it may be possible to reduce postoperative pain intensity or lower postoperative analgesic requirements for periods much longer than the strictly pharmacological duration of action of the analgesics themselves. It thus becomes possible to direct treatments not only to the site of peripheral tissue damage, but also to CNS mechanisms. Furthermore, it may be possible in some instances to actually prevent the development of central changes which contribute to pathological pain states. In this regard, the effectiveness of behavioral, hypnotic, and cognitive coping skills approaches to pain management may involve this kind of neurophysiological preemption of permanent pain memory traces.

Coderre et al. [10] theorize that, in addition to altering membrane permeability and producing immediate electrophysiological changes, noxious stimulation may result, over longer periods of time, in increased expression of proto-oncogenes such as c-fos, the protein products of which act as third messengers. Following noxious stimulation, there is an increased expression of c-fos in CNS structures involved in pain transmission, including the periaqueductal gray, thalamus, habenula, and somatosensory cortex. C-fos is involved in the transcriptional control of the dynorphin and enkephalin genes, and its expression following noxious stimulation leads to an increased synthesis of dynorphin and perhaps enkephalin. In this way, dynorphin may have complex effects modulating the development of central plasticity and hyperalgesia in various ways.

Thus, activation of intracellular, molecular third messenger systems in response to sensitization is invoked as an explanatory mechanism in both Post’s [42] model of affective disorder and Coderre et al’s [10] model of pathological chronic pain. It is not difficult to conclude that the vicious cycles of agony and despair we see and treat in our patients reflect the operation of this kind of “out-of-control” positive feedback loop, one of the factors that makes chronic pain syndromes so difficult to treat.

4. Posttraumatic stress disorder

Painful injuries in civilian life typically have their origin in some form of traumatic event such as traffic, worksite, or assault injury. In such cases, psychological traumatization may accompany physical injury, or it may be the sole enduring effect of the injurious event.

Clinically, the PTSD patient is constantly on the alert, hypervigilant to real and imaginary dangers. He sleeps poorly and is easily distractible. He is subject to repeated intrusive thoughts about, images of, and associations to, the trauma. The patient may show memory disturbances to the point of virtual amnestic and dissociative states. He complains of being estranged from other people; the world and its inhabitants appear hostile, uninteresting, remote, or changed. His capacities for intimacy, tenderness, and passion are lost, and irritation and anger are poorly controlled. He is preoccupied with the trauma, either through constant reminders, flashbacks while awake, nightmares during sleep, impairment of daily activities, unemployment, or disfiguring physical scars from associated injuries. At the same time, he takes great care to avoid being reminded of the traumatic event [27,30,36,37,56].

PTSD is so frequently comorbid with other disorders, such as chronic pain, postconcussion syndrome, depression, and somatoform disorders [31,34], that “pure” chronic PTSD would seem to be the exception, not the rule, supporting the concept of a cascade of events, the most common of which is the original trauma. The cascade may be initiated by either the original trauma or by the PTSD itself [2,3].

Charney et al. [9] have elaborated a psychobiological model of PTSD that appears to characterize it as a neurosensitization syndrome. According to this model,
sensitization by fear associated with traumatic stress results in a change in excitability of amygdaloid neurons. This in turn influences the functioning of a variety of limbic and brainstem structures involved in the somatic and autonomic expression of fear and anxiety. For example, a reduced activation threshold of the locus coeruleus results in increased norepinephrine output at locus coeruleus projection sites. In addition, functioning in mesocortical dopaminergic neurons is elevated.

Stress-induced impairment of long-term potentiation, mediated in part by excitatory amino acid, noradrenergic, and opioid receptor systems, may be responsible for the development of the learning and memory deficits observed in PTSD. Because extinction appears to involve an active learning process—an idea that goes back to Pavlov [38]—deficits in learning may impair normal extinction in patients with PTSD, leading to the abnormal persistence of emotional memories. This may partially explain the “paradox” of learning and memory deficits coexisting with abnormally intense intrusive recollections in PTSD.

Further, locus coeruleus activation of the amygdala enhances memory retrieval. This memory-enhancing effect of increased noradrenergic activity may be mediated by beta-adrenergic receptors within the amygdaloid complex. By this mechanism, some of the acute neurobiological responses to trauma may facilitate the encoding of traumatic memories.

In patients with PTSD, specific sensory phenomena, such as sights, sounds, and smells circumstance-related to the traumatic event, persistently produce a recrudescence of traumatic memories and flashbacks. The brain regions mediating these processes include the amygdala, locus coeruleus, hippocampus, and sensory cortex. Most of the evidence points to the amygdala as particularly important in the conditioning and extinction of sensory and cognitive associations to the original trauma and subsequent activation of traumatic memories. N-methyl-D-aspartate (NMDA) receptors on the amygdala are inferred to be involved in these processes because NMDA antagonists applied to the amygdala and NMDA lesions of the amygdala prevent the development of fear-conditioning responses and the extinction of fear-precipitated startle.

Thus, the amygdala functions to attach fearful or anxious affect to neutral stimuli associated with the trauma. The functional interchange between the amygdala and the sensory cortices, where memories of each sense are stored, may be critical for the ability of specific sensory to elicit traumatic memories. In addition, activation of the amygdala may also be responsible for the highly correlated set of behaviors associated with traumatic memories. As an aside, it is interesting to note that behavioral automatons are a frequent manifestation of seizures originating in temporal or frontotemporal limbic areas.

The continued revivification of traumatic memories associated with a painful injurious event may thereby act as both trigger and reinforcer of chronic pain as a coping response to trauma. It is noteworthy that, just as early postsurgical alleviation of physical pain is associated with a lower incidence and severity of chronic pain behavior, early application of arousal-reducing pharmacological or behavior modalities following psychological trauma can significantly reduce the extent and severity of later PTSD reactions [8,16].

5. Treatment implications

All of the neurosensitization syndromes discussed here share a conceptualization of interaction based on a pattern of maladaptive positive feedback that eventuates in a pathological outcome. All of the models imply a certain plasticity in the adult CNS at (at least) three different levels: (1) neuropsychological: cortical perceptual-evaluative vs. limbic emotional-reactive; (2) neurophysiological: exemplified by the phenomenon of synaptic reorganization or kindling, but presumably also characterized by varying, often more subtle, degrees of electrophysiological sensitization; and (3) molecular-genetic: for example, as alterations in the action of intracellular third messenger systems, leading to longer-term changes in neuronal functioning and thereby in experience and behavior.

Psychotropic and pain medication is often the first stopgap method for treating traumatic disability syndromes, with little evidence of long-term effectiveness when used in isolation, even for specific symptoms, such as anxiety or depression [13]. Given that the formation of neurosensitization syndromes involves complex brain-environmental interactions at many psychobiological levels, it is difficult to imagine how the administration of single classes of pharmacological agents could do more than provide partial and transitory symptom relief.

Of course, symptoms relief per se should hardly be eschewed as a therapeutic objective, as it often provides a necessary first step to further treatment, not to mention being life-stabilizing in many cases. But the most effective therapeutic interventions probably need...
to be of equivalent neuroexperiential complexity as the original pathogenic set of events. Hence, just as the efficacy of properly applied psychotherapy has been clinically and empirically demonstrated to be equal or superior to drug treatment for many kinds of mental disorder \([4,53]\), so for most cases of neuropsensitization syndrome, appropriately targeted psychotherapy is the treatment of choice for traumatic disability syndromes, especially with regard to effecting long-term change \([32]\). Perhaps, as Dubovsky \([13]\) asserts, the therapeutic relationship “splints” the neurophysiological regulatory mechanisms, providing a repeated corrective stabilization, so that they can eventually function normally on their own. This may explain why even long-term, seemingly entrenched “organic” syndromes such as chronic pain, postconcussion syndrome, toxic trauma, and other traumatic disability syndromes often respond quite favorably to appropriate psychotherapy applied by skilled clinicians \([31,32]\).

The present neuropsensitization model of traumatic disability syndromes should be taken as a first step, not the last word. In building neuropsychological models of complex clinical phenomena, the dangers of oversimplification and premature reification can hardly be overemphasized. For now, what the concept of neuropsensitization can offer the field of traumatic disability syndromes is to demonstrate that behavior is never static, that human nature at all its psychobiological levels can always be influenced for good or ill by the world around us and the people in it.

References


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