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A Review: Detail Pharmacology of Pain, Different Method of Pain Assessment and Management in Patient

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ABSTRACT
Pain sensation involves multiple signaling and modulatory pathways, employing a variety of neurotransmitters and other mediators. Inhibitory and facilitatory mechanisms affect the perception of stimuli as painful or non-painful, and in addition may affect the perceived intensity of pain. Endogenous opioids are key mediators in the descending pain suppression pathways. Additionally, monoaminergic neurotransmitters such as norepinephrine, serotonin and dopamine positively or negatively modulate pain signaling, depending on receptor type and location. The various mediators involved in pain signaling provide potential targets for pharmacological interventions. Single analgesic therapies may be limited in their ability to comprehensively target these complex pain signaling pathways. Therapeutic approaches acting on multiple pain transmission pathways through different mechanisms of action provide an opportunity to maximize efficacy and tolerability in the treatment of pain.

KEY WORDS
Pain, signalling pathway, modulatory pathway,pharmacological and non pharmacological method, analgesic, non steroidal anti inflammatory, neuroimaginary method

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SCOPE

This article discusses the various physiologic processes involved in pain signaling and modulation, describes the mechanisms by which various classes of analgesic agents are believed to produce their clinical effects, and explores the potential benefits of a multiple-mechanism approach to analgesia. Published articles describing the physiologic processes involved in pain signaling and modulation and the mechanisms of analgesia for different drug classes were reviewed. Along with this also discuss about various pain assessment tools and pain management in patient by different pharmacological and non pharmacological method. Also suggest some check point and current prospects and advancements in neuroimaging of pain.

I. Introduction

Pain is a highly complex and individual experience with biological, psychological and social (biopsychosocial) contributions. Pain is associated with activity within the nervous system – peripheral neurons and receptors, central spinal neurons, interneurons and receptors, as well as supraspinal components of the brainstem, midbrain, subcortical structures and cerebral cortex. The study of pain within the central nervous system (CNS) using neuroimaging is a large and growing area of research. By non-invasively studying the CNS using neuroimaging in healthy human volunteers and individuals with chronic pain, we now understand that pain processing involves an integrated network of regions and mechanisms throughout the body. The focus of this review is to provide an update on knowledge of pain that has been acquired by neuroimaging the CNS and to highlight important contributions to the field. It is not meant to be an exhaustive or systematic review, but rather, comprehensive enough to provide the practicing anesthesiologist and pain clinician a current human neuroimaging perspective of CNS processes related to acute and chronic pain. We also include a brief

description of selected neuroimaging research of pharmacological and psychological modulation of pain; these studies are informative regarding how pain, and its CNS correlates, can be altered (for better or for worse) by both endogenous and exogenous influences. We discuss how knowledge from the field of pain neuroimaging is relevant for informing clinical practice and for providing a framework for understanding the complex contexts of the pain experience. Finally, we discuss future directions in the use of neuroimaging based treatments and how brain based biomarkers may help us achieve the goal of personalized pain management.

1. Current Neurophysiological Conceptual Framework of Pain

In the classic acute pain experience, noxious stimulation evokes nociceptive signals which are transmitted to the cerebral cortex via a series of complex multi-mechanistic pathways (for review:[1]). Receptors in the periphery (e.g., skin and body tissues) transduce mechanical, thermal and chemical stimulation from the environment into nociceptive signals which are relayed via peripheral primary afferents to the dorsal horn of the spinal cord. There, the primary afferents synapse onto and transmit their nociceptive signals to secondary spinal neurons, which in turn, transmit nociceptive information to supraspinal regions of cortical and subcortical structures. Nociceptive information is also relayed to brainstem, midbrain and medullary regions which can modulate (amplify or diminish) the perception and sensation of a noxious stimulus. The perception of pain occurs by the activation of a network of connections within the cerebral cortex. Because of this, nociceptive input is not required for the perception of pain, and a painful experience can be elicited by brain stimulation directly. Furthermore, within the brain, the experience of pain is created and shaped by past experiences, context, cognitive and emotional input.

The complex processes of the pain experience and modulation within the brain are of substantial interest to the field of pain neuroimaging. The brain and subcortical structures together serve as an organ system that can reasonably well be assessed using several non-invasive neuroimaging techniques, most commonly structural and functional magnetic resonance imaging (MRI). The importance of imaging and understanding these cortical and subcortical processes lies in that these structures are major sites for pain modulation via physiological (different brain regions involved in modulating pain perception), psychological, and pharmacological (both endogenous and exogenous) modalities.

While this review focuses on a selection of neuroimaging insights about pain, we first focus our attention on two major underlying principles of the nervous system and pain processing. First, the CNS (e.g., brain, brainstem and spinal cord) is highly plastic, meaning that it is often and easily altered by physiological and pharmacological processes, via both exogenous and endogenous effectors. Plasticity of the nervous system has been shown through a wide range of neuroimaging and non-neuroimaging research. For example, macroscopically, limb amputation causes regional changes in somatosensory cortex representation in such a way that suggests, "alterations of sensory processing are not hardwired, but are rather mediated by an extensive and interconnected neural network with fluctuating synaptic strengths"[2]. At the other end of the spectrum, microscopically, widespread changes in neural function are associated with pruning of the dendritic spines on individual neurons (e.g.,[3]) and pronounced dendritic branching occurs after sensorimotor training in rodents[4]. Another important principle is that pain processing is distributed, in that it engages multiple brain regions during the pain experience[5]. Individual brain regions and networks (i.e., multiple brain regions with concurrent and therefore presumed complementary function) have been demonstrated to contribute to certain aspects of pain processing (e.g., affective versus sensory components). However, our understanding of how pain is processed by and within the CNS is still a work in progress. Ultimately, the knowledge that 1) the brain is highly plastic, and 2) pain processing encompasses distributed regions of the brain with various functions that modulate the pain experience, supports the appropriateness of multi-modal, multi-interventional approaches for chronic pain prevention and ideal treatment.

2. Central Nervous System Processes of Acute and Chronic Pain

Introduction to Themes of "Normal" Pain Related Brain Activity

Before discussing evidence of altered brain processes in chronic pain, we need to first discuss evidence of normal pain processes in healthy states. Hallmark studies have indicated that multiple regions of the brain are involved in sensory, affective or emotional, and evaluative aspects of pain processing in healthy individuals. These studies have used noxious and innocuous stimuli including thermal[6], mechanical (e.g., pin prick and pressure)[7], chemical (e.g., capsaicin)[8], electrical[9], and incisional pain paradigms[10] to model the pain response within the brain. While standard tonic stimuli have been most often used to study supraspinal responses to pain, several studies have employed dynamic stimuli that evoke pain phenomena such as offset analgesia[11], conditioned pain modulation (formerly termed diffuse noxious inhibitory control)[12], and temporal summation of pain[13]. As repeatedly shown across many studies, the key brain regions involved in pain processing include the primary somatosensory cortex, primary motor and supplementary motor cortices, secondary somatosensory cortex, insular cortex, anterior cingulate cortex, thalamus, as well as regions within the prefrontal and parietal

cortices and regions of emotion, memory and fear processing in the amygdala, hippocampus and subcortical structures including the basal ganglia (Fig. 1)[5,6,14–16]. Individual neuroimaging investigations often indicate pain-related brain activity within a subset of these structures; the differences in brain activity across different investigations may result from the inclusion of different participant populations, different stimulation parameters and modalities, differences in analysis methods, differences in instructions for the participants, as well as differences in psychological states of the individual subjects. It is understood that the brain regions activated during the pain experience overlap with brain regions that are activated under multiple other highly salient sensory experiences such as the presentation of visual, auditory or innocuous somatosensory stimulation[17]. Similarly, viewing others in pain (i.e., empathy of pain) engages many of the same brain regions as the actual experience of physical pain[18,19]. Thus, it is important to keep this conceptual framework of salience processing in mind when evaluating the literature. However, many investigations have contributed elegant work to deduce the main brain regions activated during the pain experience and how activity within these regions contributes to the aspects of the pain experience, as described in more detail below.

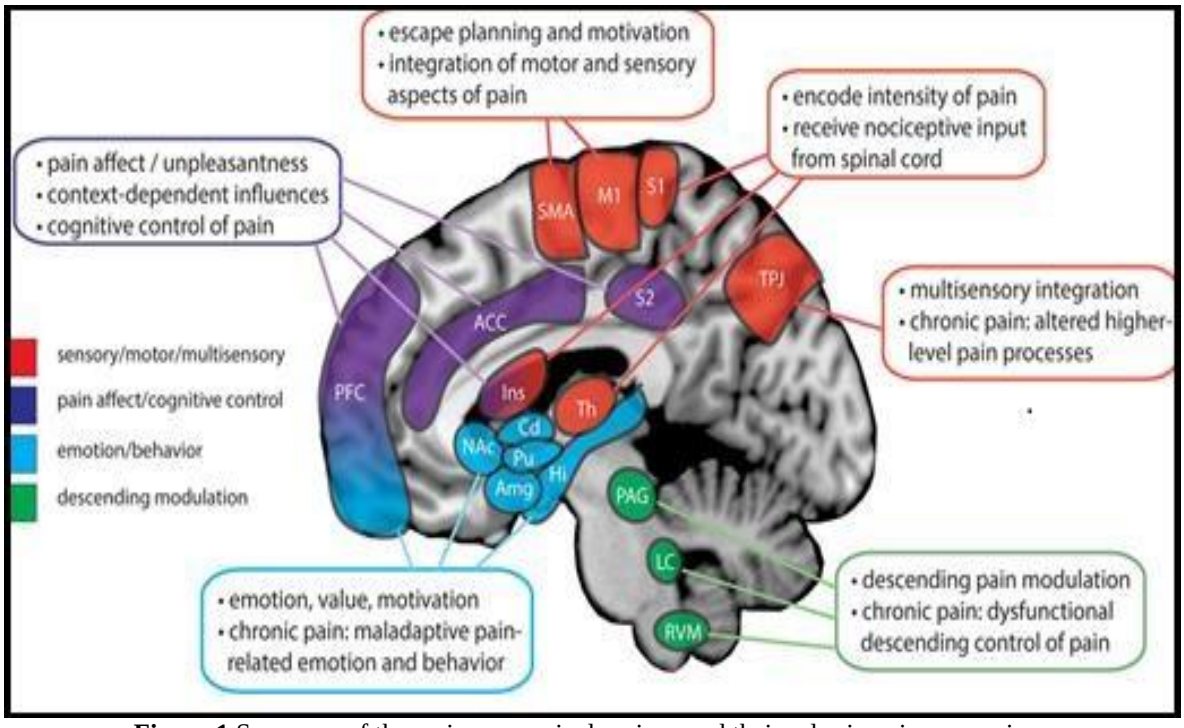

Figure 1 Summary of the main supraspinal regions and their roles in pain processing.

Multiple cortical and subcortical structures are involved in various primary roles and aspects of the pain experience (as color coded). Additional brain regions and networks not shown in the figure are involved in the pain experience - see text for details. Abbreviations: ACC - anterior cingulate cortex, Amg - amygdala, Cd - caudate, Hi - hippocampus, Ins - insular cortex, LC - locus coeruleus, M1 - primary motor cortex, NAc - nucleus accumbens, PAG - periacqueductal gray, PFC - prefrontal cortex, Pu - putamen, RVM - rostral ventral medulla, SMA - supplementary motor area, S1 - primary somatosensory cortex, S2 - secondary somatosensory cortex, Th - thalamus, TPJ – temporal-parietal junction.

Normal Pain Processes within the Brain

Brain regions receiving direct projections from spinal nociceptive neurons and processing the sensory-discriminative aspects of pain include the primary somatosensory cortex, posterior insular cortex and thalamus. Within the thalamus nociceptive inputs are modulated and then transmitted to cortical and subcortical structures[20]. The primary somatosensory cortex and posterior insular cortex are two brain regions that encode the intensity of painful stimuli, i.e., these regions increase activity in a graded fashion that corresponds to the intensity of the stimulus presented[21]. The affective dimension of pain is related to perceptive and context dependent pain processes within the brain. Classic brain regions associated with the affective dimension of pain processing include the secondary somatosensory cortex and anterior insular cortex. Activation measured within these regions corresponds to the levels of unpleasantness and context-dependent influences of the pain experience[22]. Cognitive modulation of the pain experience is thought to be driven largely by regions within the prefrontal cortex (e.g., anterior cingulate cortex, ventromedial prefrontal cortex, dorsolateral prefrontal cortex)

as noted in many studies of placebo and nocebo effects[23], controllable versus uncontrollable pain states[24], reward induced by romantic love[25], attentional distraction[26], and real-time neuroimaging biofeedback[27]. The motor and supplementary motor cortices are involved in pain processing and may be related to the motivational or escape aspects related to the pain experience[28]. Regions involved in fear, anxiety[29], and memory processing including the amygdala and hippocampus have also been noted to play a role in the pain experience[30]. Subcortical structures within the basal ganglia may be involved in the intensity discrimination, motor response, and motivational aspects of pain[31]. Brainstem, midbrain and medullary regions including the midbrain periaqueductal gray, locus coeruleus and rostral ventral medulla are involved in the descending modulation of pain, thus exerting both inhibitory and facilitatory effects on spinal circuits[32,33].

Experimentally Induced Abnormal Pain Processes within the Brain

While brain processes involved in the pain experience can be studied under healthy states, experimentally induced perturbation of pain circuits can produce temporary hyperalgesia and allodynia, thus creating human models of the symptoms typically experienced in clinical pain states. The use of topical capsaicin creams, which contain the active ingredient in hot chili peppers, activates transient receptor potential cation channel subfamily V member 1 (i.e., "TrpV1") receptors in the skin and can be used to induce a state of experimental or acute central sensitization. The classic capsaicin-heat sensitization model[34] induces temporary experimental allodynia (i.e., perception of a normally innocuous stimulus as painful) and hyperalgesia (i.e., perception of a normally noxious stimulus as more painful than normal) that can be prolonged as necessary and then diminishes soon after the completion of the study procedures. Capsaicin-induced allodynia and hyperalgesia typically results in increased activation of pain-related brain regions including the somatosensory, prefrontal, insular and parietal cortices[35]. Other studies using capsaicin application in healthy volunteers have identified altered brainstem activation[36] and changes distributed throughout the cortex that are consistent with increased pain and increased activation of countering endogenous analgesic circuit activation (e.g., descending control)[37]. Induction of hypersensitivity can also be used to contrast normal versus hypersensitive states of mechanical and thermal stimulation, indicating that each type of noxious stimulation produces a distinct signature of activations within the brain, and further distinct changes within these activations during induced hyperalgesic states[8]. Studies investigating altered brainstem activation after induction of experimental hyperalgesia[36] and altered spinal cord activity by nocebo hyperalgesia effects[38] further implicate the importance of potential non-cortical contributions to human chronic pain symptoms.

Altered Brain Structure in Chronic Pain States

Considering that pain processing is distributed across multiple brain regions, and may be, in part, dependent on processes in the brainstem and spinal cord, it is not surprising that studies of CNS activity among individuals with chronic pain have identified alterations within multiple regions and levels of the nervous system. Structural brain differences in gray matter density, gray matter volume and cortical thickness between patients with chronic pain and healthy volunteers have been noted in many types of chronic pain including chronic low back pain[39,40], fibromyalgia[41], complex regional pain syndrome[42], chronic pelvic pain syndromes[43,44], and temporomandibular pain[45,46], among others. Additionally, regional gray matter changes have been shown to reverse coinciding with effective treatment in patients with chronic low back pain[47]. These observations suggest that there is underlying structural plasticity and changes of the brain's cellular composition in individuals who experience chronic pain.

The specific underlying physiological changes contributing to the observed differences in gray matter remain in question. Decreases in regional gray matter in chronic pain have been thought to suggest more rapid aging of the brain in chronic pain[48,49], however, this explanation has been debated because regional gray matter increases have also been observed in chronic pain and do not follow logically with the aging explanation. Neuroimaging researchers have speculated that increases and decreases in gray matter may be due to changes in gray matter microstructure (e.g., changes in the number of dendritic spines and connections), and the prevalence of glial and other supporting and neuro-immune cells within brain regions, among other possible mechanisms (for review:[50]). A recent study in patients with fibromyalgia revealed evidence suggesting that regional gray matter decreases are due to decreased tissue water content and regional gray matter increases are due to increased neuronal matter and possibly inflammation[51]. However, these findings need to be further validated in other types of chronic pain and disease, and by additional complementary measures. Nonetheless, observed differences in brain structure in chronic pain implicate altered function within the CNS in patients, however, additional research investigating the underlying causes of observed differences in gray matter in chronic pain is needed.

Measurements of white matter, or axonal fiber pathways, within the brain have also provided evidence about how the brain structure and its underlying processes are altered in chronic pain. As compared with healthy states, chronic pain states of fibromyalgia[52], chronic pelvic pain[53], chronic low back pain[54], complex regional

pain syndrome[55], and visceral pain syndromes[56] have been identified as demonstrating differences in white matter integrity. The majority of these studies used a method of diffusion tensor imaging which uses properties of water molecule movement in axons to determine measure of integrity of the axon (i.e., more movement and coherence along the main direction of the axon equals better integrity of the axon fiber). Differences in the degree of fractional anisotropy, a measurement of coherence along a bundle of axon fibers, have been identified in regions of white matter indicating differences in structural connectivity between brain regions in individuals with chronic pain. For example, a study comparing white matter axonal integrity among patients with chronic pelvic pain, patients with irritable bowel syndrome, and healthy controls identified increased fractional anisotropy within the corticospinal tract in patients with chronic pelvic pain and decreased fractional anisotropy within the thalamic radiation in patients with irritable bowel syndrome[57]. These observations were correlated with symptoms of pain severity and therefore implicate changes in axonal microstructure that may be specific to these two types of chronic visceral pain. Patients with migraine, as compared with healthy controls, have been found to have lower fractional anisotropy in axon bundles within the corpus callosum suggesting regional degeneration of axonal connections in this population[58]. In these and other chronic pain conditions, the identification of regional increases and decreases in structural integrity of white matter tract connections suggests underlying enhancements and disruptions, respectively, of neural communication between the regions to which the tracts connect.

Altered Brain Function in Chronic Pain States

Neuroimaging techniques have been used to study brain functional differences in chronic pain versus healthy states. Neuroimaging studies have used fMRI extensively to study pain processing. FMRI relies on a correlate of activity due to differences in the magnetic properties of oxygenated and deoxygenated blood, known as the blood oxygenation dependent level (BOLD) signal. Several studies have investigated differences in perception of noxious stimulation in patients with chronic pain while undergoing fMRI scans. Examples of such studies include combining fMRI with the use of tests of temporal summation of heat pain in fibromyalgia[59], tests of heat pain sensitivity in complex regional pain syndrome[60] and chronic low back pain[61], and tests of mechanical sensitivity in chronic low back pain[62] and fibromyalgia[63,64]. Visceral pain studies have identified differences in brain activity associated with pain during bladder filling[65], and in response to rectal distension in patients with irritable bowel syndrome[66]. Interesting neuroimaging observations of altered brain activity within the contralateral and ipsilateral regions of the brain in patients with neuropathic pain indicate that altered peripheral afferent (incoming) information produces dramatic shifts in representation within the brain[67]. Collectively, these investigations point towards heightened responsivity of the CNS to afferent noxious and innocuous stimuli in chronic pain.

With the emergence of resting state fMRI as a technique for studying non-evoked brain activity and functional connectivity, many investigations of chronic pain have used this technique to gain understanding of brain processes more generally, as opposed to specifically related to noxious stimuli, in chronic pain. Resting state activity is based on established principles[68] identifying correlated low frequency (0.01 – 0.1 Hz) fluctuations of fMRI signals (BOLD activity) across brain regions. These principles allow for the parcellation, or subgrouping, of brain fMRI data into functional networks of regions that appear to "work together", operating and contributing to related functions. Functional connectivity is the degree of correlated activity, based on the BOLD signal, among and between brain regions and networks. Based on these principles, several studies have used resting state fMRI to characterize differences in non-evoked (i.e., resting) brain activity among patients with chronic low back pain[69], fibromyalgia[70], chronic pelvic pain syndromes[71], complex regional pain syndrome[72] and others. Several resting state studies of chronic pain have identified alterations in default mode network connectivity, a network of brain regions including the precuneus, posterior cingulate cortex, medial prefrontal cortex and angular gyrus. The default mode network is more active at rest, suggesting that this network might be in a continuous hyperactive state in chronic pain[73] and possibly that regions of this network are hyper-involved with pain-related processes ongoing in the brain[71]. Other studies have focused on more regional connectivity differences specifically within brain regions involved in motor and sensory processes[65,74], emotion and fear processing[75], reward and motivation[76], and cognitive processes[77], as well as alterations in brainstem functional connectivity[78].

Additional neuroimaging techniques of nuclear magnetic resonance spectroscopy and positron emission tomography (PET) allow for identification of altered neurotransmitter/neuromodulator function within regions of the brain in individuals with chronic pain. Such studies have used PET imaging to detect decreased dopamine activity in fibromyalgia[79,80] and decreased opioid receptor binding potential in fibromyalgia[81]. Widespread differences in measured metabolite and neurotransmitter function, including N-acetylaspartate and glutamate, have been identified in in chronic low back pain using proton magnetic resonance spectroscopy (for review:[82]). Similarly, reduced N-acetylaspartate levels in prefrontal cortex have been observed in patients with complex regional pain syndrome[83]. Altered N-acetylaspartate observed in regions such as the prefrontal cortex

and somatosensory cortex of patients with chronic pain suggests possible degradation of receptors within these brain regions. In fibromyalgia patients, increased glutamate within the posterior insular cortex, a region implicated in the sensory-discriminative dimension of pain processing (e.g., pain intensity), is correlated with levels of pain sensitivity[84], and levels of insular cortex glutamate co-vary with levels of pain measured pre and post effective treatment[85]. Collectively, such observed differences in metabolite and neurotransmitter function in patients with chronic pain complement structural and functional MRI evidence in chronic pain.

Combining Neuroimaging with Immunology and Genetics for the Study of Chronic Pain

Neuroimaging technology can now identify immune changes within the CNS (for review:[86]). PET imaging combined with a radioligand specific for detecting glial cell reactivity has identified increased glial reactivity within multiple brain regions, including somatosensory cortex and thalamus, in patients with chronic low back pain, as compared with healthy control subjects[87]. By combining neuroimaging and genetics data, subgroups of chronic pain states are starting to be identified based on their genetic and regional brain activity profiles. For example, in a study of women with primary dysmenorrhea, individuals with the G allele OPRM1 A118G polymorphism demonstrated decreased functional connectivity between the anterior cingulate cortex and periaqueductal gray, regions involved in descending modulation of pain[88]. As these types of studies continue to be performed, they will continue to advance our understanding of the links between neural processes, immune states, and genetic profiles.

Longitudinal and Multi-Modal Neuroimaging Investigations of the CNS in Chronic Pain

To date, the majority of chronic pain neuroimaging investigations are not longitudinal studies. Therefore, it cannot be determined whether observed differences in brain structure and function are pre-existing to the chronic pain condition, suggesting an underlying predisposition to acquire a chronic pain condition, or whether these differences were caused by or are the direct cause of the chronic pain condition itself. This issue represents one of the main limitations of neuroimaging, and a summary of additional limitations and benefits of neuroimaging methods for chronic pain are provided in Table 1. Nonetheless, a few longitudinal studies exist, and these studies suggest that the changes in brain structure and function are linked to presence and ongoing burden of the chronic pain condition and mirror the compounding effects of negative social and emotional factors over time[89,90].

Table 1: summary of additional limitations and benefits of neuroimaging methods for chronic pain

Neuroimaging Benefits and Limitations
Benefits and Uses
Non-invasive (MRI, fMRI, MR Spectroscopy) identification of brain structural and functional alterations
Variety of measurements and applications:
• MRI: gray matter and white matter structure
• fMRI: stimulus-induced and task-based activity and resting state functional connectivity (BOLD signal dependent), manipulation of cognitive and behavioral states
• Positron emission tomography (PET): pharmacological based function (e.g., neurotransmitter estimates / receptor availability for endogenous opioids, dopamine and other metabolites)
• MR Spectroscopy: neurotransmitter and metabolite concentrations (e.g., glutamate, N-acetylaspartate)
Limitations
Limited causal inference of observed group differences (improved interpretation with longitudinal and pre/post intervention designs)
Large immobile equipment required (MRI / PET scanner), expensive (average $500 per hour)
PET imaging is invasive, involving radiotracer injection and arterial blood sampling.
Potential artifacts in images (e.g., due to head motion, physiological noise from cardiac and respiration influences, magnetic field inhomogeneity at air/tissue interfaces)
Limited resolution (i.e., > 1mm) and fMRI signal based on correlates of blood flow, indirect measure of neural activity.
Ineligibility due to MRI contraindications (e.g., metallic implants, claustrophobia, pregnancy)
Requires post-processing of images prior to analysis and multi-step analysis using specialized software

Additional insightful research findings are now emerging from the use of multi-modal imaging. Multi-modal imaging combines the use of multiple types of neuroimaging data with the goal of identifying complementary structural and functional brain alterations. The degree of overlap between differences identified by each modality can enhance the certainty of validity and meaningfulness of the brain alterations identified. For example, complementary brain structural alterations of gray matter density and white matter axonal integrity have been identified in patients with complex regional pain syndrome within regions of the insular cortex,

prefrontal cortex and basal ganglia[55]. Similar multi-modal studies have been conducted in fibromyalgia[52,91] as well. As an example of complementary functional and structural brain alterations, differences in resting state functional connectivity and white matter axonal integrity, centered around regions within the insular and prefrontal cortex, appear to underlie disrupted cognitive processes in patients with chronic low back pain[54]. These findings demonstrate how complementary regional alterations in brain structure and function provide a more complete picture for understanding how the CNS is altered in chronic pain.

Neuroimaging Pharmacological and Psychological Modulation of Pain Processing

In addition to measuring brain structural and functional differences in patients with chronic pain, neuroimaging is a tool that can increase our understanding of how medications alter CNS activity in response to pain (acute or chronic). One goal of neuroimaging neuro-pharmacological research is to clarify how medications work to reduce the sensory and affective impact of chronic pain and comorbid symptoms including anxiety and depression. Currently, the global and regional impacts on CNS by medications used to treat chronic pain are generally unknown. Furthermore, medications are prescribed by clinicians for individual patients primarily in a trial-and-error fashion[92]. Pharmacological studies using neuroimaging can allow for elucidation of the mechanisms of action of medications that will guide development of future treatments. For example, reduced activity within the medial prefrontal cortex, a region involved in cognitive control of pain, has been shown to mediate decreases in mechanical pin-prick hyperalgesia after systemic administration of lidocaine in healthy individuals[93]. While our knowledge of CNS mechanisms of anti-nociception is still incomplete, advances in research combining clinical trials and neuroimaging may someday provide data to inform clinical practice. For example, neuroimaging may help to predict which patients may benefit more from a specific medication or therapy, thereby achieving the ultimate goal of personalized medicine. This has recently been demonstrated[94] in the treatment of depression where amygdala activity combined with knowledge of early life stress was able to predict treatment response to an antidepressant with greater than 80% accuracy.

Recent neuroimaging research has shown that opioid medications produce widespread and rapid alterations in brain structure and function. In patients with chronic low back pain, structural brain changes occur rapidly, within one month of taking opioid medications. These changes include regional increases and decreases in gray matter density, which are slow to be reversed after discontinuing opioids (no changes observed at 6 months post-opioid cessation)[95,96]. Another study of pain-free individuals taking opioid medications demonstrated structural and functional differences across the brain as compared with pain-free individuals not taking opioids[97]. While the specific neurophysiological mechanisms underlying these opioid-induced brain changes are unknown, the consequences are of considerable interest and therefore call for further study.

Neural correlates of anti-nociception by antidepressants have been investigated using fMRI in patients with chronic pain. Analgesic effects of the serotonin norepinephrine reuptake inhibitor, milnacipran, in fibromyalgia may be due to reversal of altered default mode network activity as evidenced by increased posterior cingulate cortex (a core region of the default mode network) activation observed in patient responders[98]. Another study of milnacipran in fibromyalgia identified reduced functional connectivity between anti-nociceptive brain regions of the anterior cingulate cortex and periaqueductal gray, both regions of pain modulation, to the insular cortex, a region involved in both sensory and affective processes of pain[99]. Notably, decreases in the functional connectivity between these regions in patients with fibromyalgia were related to reductions in pain after administration of milnacipran. More recently a study using magnetic resonance spectroscopy identified ventricular lactate as a putative biomarker for milnacipran efficacy in fibromyalgia and thereby suggested that drug effects may occur by reducing glial reactivity and neuroinflammation within the CNS[100]. A study of brain activity changes associated with anti-nociceptive properties of the tricyclic antidepressant, amitriptyline, indicated that this treatment acts on reducing activity within the anterior cingulate cortex to reduce pain during a stressful experience of rectal distension in individuals with irritable bowel syndrome[101].

The brain mechanisms by which anticonvulsants, such as gabapentin and pregabalin, may be beneficial for treatment of chronic pain have also been studied. Gabapentin has been shown to increase cortical neurotransmitter levels of gamma-aminobutyric acid, but not glutamate, within the brain's occipital lobe after 1 month of treatment[102]. Research conducted in healthy volunteers has shown that a single oral dose of gabapentin, as compared with ibuprofen, reduced experimentally-induced secondary hypersensitivity (increased sensitivity to mechanical stimulation surrounding the directly sensitized skin) and partially reversed sensitization-induced increases in functional connectivity between pain-associated regions of the insular cortex, thalamus and somatosensory cortex[103]. In patients with fibromyalgia, pregabalin has been shown to reduce glutamatergic activity within the posterior insula, a key brain region involved in processes of pain[104]. Additionally, this study demonstrated that pregabalin administration reduced aberrant increased functional connectivity between the insula and default mode network brain regions. These changes were correlated with efficacy of pregabalin among the patients, and baseline neuroimaging measurements were predictive of

responders and non-responders. Neuroimaging has even been used to identify changes in brain function pre and post treatment with ketamine for complex regional pain syndrome, further implicating the highly plastic nature of the brain in response to therapy[105].

Neuroimaging additionally provides a method for investigating neural correlates of effective psychological therapies. Chronic pain often presents with patients having deficits in cognitive and emotional control particularly relating to their experience of pain (for review:[106]). Effective psychological therapies for pain strengthen practices of healthy psychology thereby reducing the negative impact of chronic pain. Such therapies include cognitive behavioral therapy, acceptance and commitment therapy, mindfulness based stress reduction, and mindfulness meditation. These types of treatments can benefit individuals suffering from chronic pain by reducing negative emotional, cognitive, and behavioral responses to pain and thereby improving pain-related outcomes[107]. Neurophysiologically, psychological-based therapies including cognitive behavioral therapy and acceptance and commitment therapy reduce an individual's perceived severity of chronic pain via increased prefrontal cortex activity. Increased prefrontal cortex activity after cognitive behavioral therapy and acceptance and commitment therapy treatment implicate enhanced cognitive control of one's psychology[108] in agreement with earlier proposed neurological correlates of pain control[109]. Mindfulness based stress reduction and mindfulness meditation are somewhat similar in practice and may therefore exert positive effects on the chronic pain experience via similar neurophysiological processes. Meditation reduces pain and decreases activity within the prefrontal cortex[110,111], and may assist in reducing the affective component of the pain experience by decreasing maladaptive cognitive processes of rumination and catastrophizing. Mindfulness meditation induces analgesia by recruiting increased activity within the anterior cingulate cortex and the anterior insula, additional regions involved in the cognitive regulation of pain[112]. Positive expectations and beliefs, underlying placebo effects, are powerful psychological modulators of the pain experience and involve similar brain regions involving cognitive control of pain[23,113]. Neuroimaging research in these areas continues to determine the how psychology interacts with the pain experience, and may in the future, aid in optimizing psychology-based therapies for individuals with chronic pain.

Clinical Relevance for Prevention and Treatment of Chronic Pain: Neuroimaging-based Implications and Therapies

Understanding how neurophysiology is altered in chronic pain and how it can be changed through effective treatment of pain, in itself, provides an intriguing set of questions. However, the main purpose for understanding these neurophysiological changes is to better treat patients suffering from chronic pain. Neuroimaging of acute and chronic pain has provided the field of pain research and clinicians with an important framework of understanding: that even though no bodily signs of injury or dysfunction may be observed in the patients, neurological differences have been observed in brain structure and function in patients across a wide variety of chronic pain conditions as compared with healthy individuals. These observations provided by neuroimaging research together provide strong evidence that the effective prevention and effective treatment of chronic pain must include considerations of cortical and subcortical CNS processes.

Just as pre- and perioperative best practices are suggested to reduce the instance of post-operative pain, for example local anesthetics prior to limb amputation[114] or the use of gabapentin perioperatively[115], clinical research aims to identify best practices for non-perioperative pain prevention and treatment. These best practices as informed by preclinical research, clinical research, clinical trials, and neuroimaging research include a multi-modal approach of prevention and therapy. Typical approaches to treating pain include pharmacologic, procedural, psychological, physical therapy, complementary and alternative medicine, and self-management. The comprehensive multi-modal approach utilizes 1) physiological treatment and positive stimulation of the peripheral nervous system and musculature, 2) psychological treatment to engage healthy cognitive and emotional processes in the presence of chronic pain, 3) pharmacological therapies to prevent and/or reverse aberrant activity within the CNS, and 4) alternative and complementary treatments and therapies as deemed beneficial for the patient. With even broader treatment implications, neuroimaging research of chronic pain has provided evidence for clinical treatment considerations of immunological dysfunction within the CNS, as described above[87]. Such neuroimaging-based evidence further encourages increased communication between pain clinicians and medical specialists from other fields, including psychology, immunology and nutrition. Ultimately, with this multi-modal treatment approach, it is important to consider the evidence of cortical and CNS alteration and dysfunction in treatment selection approaches.

Thus far, the primary influence of pain neuroimaging on clinical practice appears to be through changing the conversation regarding pain. Neuroimaging technologies have broadened the current understanding of acute and chronic pain processes in humans, and thus have allowed for new considerations and conversations between clinicians and their patients. Probably the most influential aspect of neuroimaging enhancing the conversation of pain, for patients and clinicians, is the now vast amount of neuroimaging evidence supporting structural and functional CNS alterations in patients with chronic pain.

While many people with chronic pain present with pain that is disproportionate to any physiological manifestation of injury in the body, neuroimaging evidence indicates that the CNS is altered in these patients. Clinicians can use neuroimaging evidence as a grounds for talking points with their patients in conversations that scientifically validate the patients' pain as being real. Further, these types of conversations provide the patients with an, albeit still currently incomplete, understanding of why they may be experiencing chronic pain – because their CNS is altered such that it is creating an aberrant experience of pain within the brain and/or disproportionately responding to incoming sensory information. Thus, neuroimaging research in the field of pain has provided a context of brain and CNS physiology for understanding and discussing chronic pain symptoms in patients. In addition to providing talking points for clinicians to patients, neuroimaging evidence has provided grounds for education of medical professionals, patients, researchers, and the general population that chronic pain affects multiple systems including the CNS. Therefore, in light of this understanding, it follows that effective treatment strategies for chronic pain need to be comprehensive. Treatment should consist of therapeutic approaches targeted at multiple systems including psychological, physiological, and pharmacological therapies, combining therapeutics from conventional and alternative medicine.

Neuroimaging, of noxious stimulation in healthy volunteers and patients with chronic pain, has provided a helpful framework for thinking about chronic pain and talking about pain with patients, clinicians, neuroscientists and the public. Further, it has provided methods for increased understanding of drug mechanisms acting centrally, and the associated changes in brain structure and function that occur in response to pharmacological therapies. Neuroimaging studies have also provided evidence for how psychological and behavioral therapies are associated with changes in brain structure and function; this evidence aids us in understanding how these therapies proactively modulate the pain experience, and supports their usefulness and credibility as valuable complementary therapeutics.

Regarding actual changes in clinical practice via advanced therapeutics, neuroimaging-based therapies for pain are currently being used in clinical trials and clinical practice, as adjunct treatments where available. However, these therapies are still being used on a somewhat experimental basis. Neuroimaging-based therapies including transcranial direct current stimulation[116,117], transcranial magnetic stimulation[118,119], deep brain stimulation[120], and real-time fMRI neurofeedback[27,121] are under evaluation in ongoing clinical trials. Advancements of these technologies by supplementation of additional neuroimaging-based technologies, specification of ideal parameters, identification of novel and effective target brain regions, and individual patient predictors of success (such as differences in brain connectivity identified using neuroimaging) may lead to enhanced efficacy of neuroimaging-based therapies for individual patients in the not so distant future.

PAIN ASSESSMENT TOOLS AND PAIN MANAGEMENT IN PATIENT

Pain in critically ill patients is often under diagnosed and undertreated. In this population, there are many potential barriers to pain recognition and management. Untreated and neglected pain may contribute to increased morbidity and mortality. Assessment of pain in the intensive care unit (ICU) can be difficult; many critically ill patients cannot communicate their discomfort because of intubation, sedation, or cognitive impairment. However, in its "Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the Intensive Care Unit," the Society of Critical Care Medicine (SCCM) recommends that pain be routinely monitored in all adult ICU patients. Unfortunately, it is difficult to estimate the incidence of pain in critically ill patients because pain assessment tools and protocols for the management of pain are rarely applied. A Canadian study of 51 ICUs found that less than 20% of ICUs used pain assessment tools and only 25% of ICUs used pain protocols. A separate multicenter observational study found that 90% of patients in the ICU were being actively treated with opioids whereas only 42% had undergone a pain assessment. Similarly, Payen et al reported that pain was not assessed in 53% of patients who were receiving analgesia, and when pain was assessed, specific pain tools were used only 28% of the time.[122-124]

"It is difficult to estimate the incidence of pain in critically ill patients because pain assessment tools and protocols for the management of pain are rarely applied."

However, studies have aimed to quantify the incidence of pain in critically ill patients. We know from prospective descriptive studies that the presence of an endotracheal tube has been reported as a constant source of discomfort at rest and that routine procedures—such as tracheal suctioning, position changes, and line removal—cause pain.[125] One study suggested that pain is frequent with an incidence of 50% in medical and surgical patients at rest and 80% during common care procedures.[126] Another study showed similar results when patients recently discharged from the ICU were interviewed about their pain during hospitalization. Nearly 50% of patients reported recall of pain during their ICU stay. Fifteen percent of ICU patients reported extremely severe pain or moderately severe pain occurring at least half the time. Not surprisingly, nearly 15% of patients were dissatisfied with pain control during their ICU stay.[127] Another study showed that 63% of patients received no analgesics before or during painful procedures.[128]

Why Should We Care?

In the article "Pain Management: A Fundamental Human Right," Brenan et al wrote, "Unreasonable failure to treat pain is viewed worldwide as poor medicine, unethical practice, and an abrogation of a fundamental human right."[129] FaberLangendoen et al wrote, "Many believe the obligation of clinicians to tend to patients' suffering is the essence of the medical profession." In addition to the ethics of pain management, medical outcomes are improved when pain is optimally managed.[130]

Table 2: *Critical care pain observation tool.*

Behavior	Patient response	Score
Compliance with ventilator	Tolerating ventilator	0
	Coughing but tolerating	+1
	Fighting ventilator	+2
Facial expression	Relaxed, neutral	0
	Tense	+1
	Grimacing	+2
Body movements	No movements	0
	Protection	+1
	Restlessness	+2
Muscle tension	Relaxed	0
	Tense/rigid	+1
	Very tense/rigid	+2

Table :2 criical care pain observation tool

Pain assessment in patients on mechanical ventilation has been independently associated with a decrease in hypnotic drug dosing, duration of mechanical ventilation, and duration of ICU stay.[131] Pain contributes to hypoventilation and reduced cough, which increases atelectasis and sputum retention. These mechanisms are thought to be responsible for the increased rate of ventilator-associated pneumonia (VAP) in patients who are not routinely assessed for pain. Payen et al demonstrated decreased risk of VAP in patients routinely assessed and treated for pain.[131] Chanques et al validated those findings when they reported significantly decreased risk of VAP and duration of mechanical ventilation when pain was routinely assessed and treated.[132] Without using validated pain assessment tools and protocols, patients in the ICU are often managed inappropriately with sedation medications. Continuous sedation, titrated to a light level and with daily sedation interruptions, has been associated with an increased duration of mechanical ventilation and ICU length of stay when compared to sedation-free protocols.

Less sedative medication allows for early mobilization, which in turn results in improved outcomes. In studies designed to compare standard of care versus early mobilization of ventilated patients, patients who were randomized to early mobilization had shorter ICU and hospital lengths of stay and were less likely to die or be rehospitalized in the year following their critical illness.[133-134]

Table 3: *Behavioral pain score.*

Behavior	Patient response	Score
Compliance with ventilator	Tolerating ventilator	+1
	Coughing but tolerating most of the time	+2
	Fighting ventilator	+3
	Unable to control ventilation	+4
Facial expression	Relaxed, neutral	+1
	Partially tightened	+2
	Fully tightened	+3
	Grimacing	+4
Upper limb movements	No movement	+1
	Partially bent	+2
	Fully bent with finger flexion	+3
	Permanently retracted	+4

Table:3 Behavioural pain score

Other potential acute negative effects of untreated pain include delirium, self-harm from accidental removal of lines or tubes, sympathetic activation with increased catecholamine release leading to tachycardia and increased systemic vascular resistance, increased cardiac workload leading to oxygen supply demand mismatch, and myocardial ischemia.[135-136] In addition to acute negative health effects, untreated and undertreated pain has been associated with the development of chronic medical issues, including chronic pain, long-term psychological illness, and lower quality of life.[137-138]

How Should We Assess Pain in the ICU?

Two sensitive and validated measures are used to assess pain in patients unable to communicate their pain: the Critical Care Pain Observation Tool (CPOT) and the Behavioral Pain Score (BPS).CPOT evaluates four behaviors—facial expressions, body movements, muscle tension, and compliance with the ventilator for mechanically ventilated patients or vocalization for nonintubated patients—rated on a scale of 0–2 with a total score ranging from 0–8 (see Table 4).

Sub-scale	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Table:4 - Critical Care Pain Observation Tool (CPOT) and the Behavioral Pain Score (BPS)

BPS evaluates three behaviors—facial expressions, upper limb movements, and ventilator compliance—rated on a scale of 1–4 with a total score ranging from 3–12 (see Table 5).

Critical Care Pain Observation Tool

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
OR	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2

Table 5: Critical care pain observation tool (CPOT)

The SCCM makes numerous recommendations about treating pain in the ICU. They acknowledge the presence of pain at rest and in routine care, and they make recommendations that pain be routinely monitored using BPS or CPOT for patients who are unable to self-report.[139] They emphasize that validated scoring systems should be used to assess pain and state that changes in blood pressure and tachycardia should not be routinely used as measures for assessment of pain.[140] For more information regarding the SCCM recommendations, refer to the SCCM pain, agitation, and delirium guidelines as well as the ABCDEF bundle for prevention of postintensive care syndrome.

Aside from difficult assessment of pain in the critically ill patient, there are many other obstacles to pain management in the ICU patient.

ICU Pain Management

Appropriate assessment of pain must be partnered with an adequate, multi-modal, and evidence-based management strategy. This multi-modal strategy should incorporate both pharmacologic and non-pharmacologic modalities of pain control. The recommended approach is to employ an inclusive assessment and management protocol, which directs recommended pain management strategies based on pain scores.[141] In this section, we will discuss currently recommended pharmacologic and non-pharmacologic pain management strategies.

Non-Pharmacologic Management

There have been several non-pharmacologic methods that have gained increasing evidence over the last several years. The SCCM ICU Liberation Bundle[141] recommends four primary non-pharmacologic methods: massage therapy, cold therapy, music and sound, and relaxation therapy

The goal of non-pharmacologic therapies is to address both physical sensory pain pathways (massage therapy, cold therapy) as well as the emotional, affective and cognitive elements of pain perception (music and sounds, relaxation therapy). A challenge in critically ill patients is in many cases they are unable to communicate their sensations, perceptions or emotions surrounding their pain. However, many of these methods have been shown to decrease both self-reported pain scores and behavioral pain assessments.[141]

a. **Massage Therapy**

Massage therapy for ICU patients typically involves massage on the back, feet and/or hands. Depending on the patient's clinical status, hands-only massage is also acceptable.[142] The ICU Liberation Bundle recommends at least 20 minutes of light pressure massage at least twice in a 24-hour period.[141] Massage therapy, when done consistently, has been shown to reduce visual numeric pain scores by up to 2 points.[143-145]

Massage is typically paired with decreasing sensory stimuli such as dimming lights and either muting alarms or decreasing the volume and providing earplugs or an eye mask to the patient.[141] This is often seen as a barrier to implementation of a massage protocol, given frequent disruptions in an ICU setting. There have been no feasibility studies performed on the implementation of a massage protocol. The ICU Liberation Bundle recommends engagement of family members to participate in massage care with guidance from the nursing staff.[141,146]

b.Cold Therapy

Cold therapy in ICU patients for pain management has been described by applying gauze-wrapped ice packs to procedural areas pre-procedure. This can be done with or without pharmacologic analgesia. In a randomized study of patients having chest tubes removed, this was done for a period of 10–20 minutes pre-procedure until the skin reached 15º C, and was associated with a 1 point drop on a 0–10 visual scale, with effects diminishing after 15 minutes.[147-11]

c. Music/Sound Therapy

Music or sound therapy has been associated with moderate decreases in pain scores in ICU patients.[146,152-158] This intervention portends no physical risk to the patient so should be considered. The existing studies recommend at least 20–30 minutes,[159] taking in the patient's preferences into account. A randomized study of a music intervention compared to standard care or even noise reduction showed a decrease in self-reported pain scores as high as 2.6 points.[156]This is another area that is ripe for patient family involvement, as family will likely know what music the patient would best enjoy. Familiar voices have not been as wellstudied as music interventions, but from the existing data and anecdotal recounts by ICU survivors, hearing a familiar voice, especially during procedures, is considered helpful in relieving anxiety symptoms or mental stress,[160] and possibly pain.

d.Relaxation Therapy

Relaxation therapy includes techniques such as guided imagery, breathing exercises, biofeedback and self- hypnosis, with guided imagery and breathing exercises being the most frequently used in critically ill patients.[141,146] These therapies have been shown to have an up to a 2.6-point reduction in visual scale pain scores (0–10), albeit from small sample size and limited study designs.[141,146] Guided-image therapy which typically involves having the patient imagine a calm and relaxing location of their choice to take them psychologically out of the current painful environment and can sometimes utilize pre-recorded tapes instead of the bedside nurse, has been associated with decreased pain scores, less opioid use and shorter length of stay.[161,162] In cardiac surgery patients, a study of breathing exercises led by a bedside nurse demonstrated significantly lower pain scores when combined with opioid therapy compared to opioid therapy alone for chest tube removal.[163]

We recommended using a combination of these non- pharmacologic therapies in conjunction with pharmacologic therapy as needed for ICU-related pain.[146] These strategies can be compiled into a comprehensive pain assessment and management protocol that is standardized to ensure the highest quality of pain management in the ICU.

Pharmacologic Management

Pharmacologic management of pain has been the mainstay of treatment for critically ill patients. However, pharmacologic agents for pain are not without side effects, and can lead to unwanted issues such as opioid tolerance/withdrawal, and delirium. Pharmacologic management should be paired with protocolized pain assessments, and approached in a gradated fashion in response to pain scores.[141,146] SCCM guidelines recommend opioids as first-line for non- neuropathic pain, being careful to use a protocol based on pain scores for titration.[141,146] They also recommend the method of "analgosedation," which treats pain before initiating sedation therapy, and only using sedation if needed. Multi-modal adjunct therapies are recommended, such as

ketamine infusions, acetaminophen, and gabapentinoids and in some populations non-steroidal anti-inflammatories (NSAIDs), lidocaine infusions, and regional anesthesia. See Table 1 for non-opioid pharmacologic treatment options.

Using a standardized pain assessment and management protocol is associated with a more efficient use of pharmacologic pain control, with lower doses of opioids and improved self-reported numeric pain scores, although this association is not always consistent across studies, with some showing increased doses in certain populations.[164-166] In patients who were adequately assessed for pain, multi- modal adjuvant therapy use such as ketamine, paracetamol and nefopam increased, as did the use of dedicated treatment during procedures.[167-168] Unlike many of the non-pharmacologic interventions, pharmacologic pain management has several adverse effects, the most concerning being ICU delirium.[141,169-174]

- **Analgesic medications used in ICU patients**

Opioids are the main medications used for analgesia in ICU patients due to potency, concomitant mild sedative and anxiolytic effects. It can be administered by multiple routes. The commonly use opioids include Fentanyl, Remifentanil, and Morphine. The choice of opioid and the dosing should be individualized based on potency, pharmacokinetics and pharmacodynamics, adverse effect, patient comorbidities and organ dysfunction [175]

1.Morphine

It is the most frequently used medication in cancer patients. It is the standard by which other opioids are compared. Morphine is directly extracted from opium poppies; it stimulates the release of histamine which produces allergic and vasodilation-induced cardiovascular instability. Initial bolus intravenous (IV) morphine 2 mg dose administered slowly over 4–5 min then can be titrated with 1–2 mg every 10–15 min till adequate analgesia is achieved. Continuous IV morphine can be administered with an initial 2–5 mg bolus dose followed by 1 mg/h. Morphine is primarily metabolized in the liver and it is excreted through kidneys. It has active metabolites; morphine-3-glucuronide and morphine-6-gluconoride. Accumulation of these metabolites in renal insufficiency can produce opioid toxicity and adverse effects such as nausea, sedation, respiratory depression myoclonus and seizures (Table 2) [175]

1.1. Fentanyl

Fetany is a synthetic opioid that is 100 times more potent than morphine. It has far more lipid soluble property than morphine and is easily taken into the CNS. Compared to morphine, it does not cause histamine release and hence no vasodilation and hypotension, making Fentanyl the preferred choice for hemodynamically unstable patients. Its intravenous onset is immediate with a short duration of 30 min to 1 h, and it is extracted though liver. Fentanyl is given IV in 25–100 μg boluses for 1–2 min and then is repeated every 10–15 min till pain is controlled. Moderate–severe pain: a loading dose of 50–200 μg intravenously followed by 25–50 μg/hr. Is typically administered. Its administration for more than 5 days causes accumulation in fatty tissue, which is mobilized after the drug is stopped and may cause prolonged sedation [175]

1.2. Remifentanil

It is a fast-acting and an equally fast recovery drug. It is 200 times more potent than morphine. Its metabolism does not depend on the liver. Analgesia-based sedation with remifentanil is a useful option for mechanically ventilated patients, and it can be used in patients that need frequent neurological assessment. Hence, it is a drug of choice in analgosedation in ICU. It has shown a shorter duration of mechanical ventilation and quicker ICU discharge with Remifentanil compared with other opioids. It offers precise control of analgesia for painful procedures in ICU patients and has a highly predictable onset and offset, with a stable context sensitive half-time (3–10 min). Initial dose adjustment is not required for patients with impaired renal and hepatic functions. Remifentanil can be administrated in higher doses than are normally used with other opioids without concerns about accumulation and the possibility of unpredictable and/or delayed recovery. Frequently, ICU patients are managed without bolus doses, and it is recommended that remifentanil infusions should be started at 6–9 μg/kg/h and then titrated in the range dose of 0.5–15 μg/kg/h. The major adverse effects are hypotension and bradycardia (Table 2) [176]

1.3. Tramadol

It is a centrally acting opioid-like medication, acts by binding to the μ opiate receptor; it is a pure agonist and inhibits adrenaline and serotonin reuptake. The most common adverse effect includes nausea, vomiting, dizziness drowsiness, dry mouth and headache. Tramadol causes less respiratory and cardiovascular depression, euphoria and constipation. Initial bolus dosage is 100 mg. After 90 min following the initial bolus, further doses of 50 mg may be given every 30 min up to a total dose of 250 mg. Subsequent doses should be 50 or 100 mg for 4–6 h up to a total daily dose of 400 mg [176]

- **Non-opioid analgesic agent or adjuvants used in ICU patient**

Non-opioid analgesics are use in the management of mild to moderate pain and moderate to severe pain with adjunctive opioid analgesics. The potential advantages of multimodal analgesia, which involves a combination of analgesics with different mechanisms of action, include improved analgesia with a lower opioid dose required and a decreased risk of opioidrelated adverse effects [176]

1. Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have opioid-sparing effect but they are not sufficiently investigated in ICU patients. Their use in ICU patients is still controversial. The most worrying adverse effect includes gastrointestinal bleeding, renal dysfunction and inhibition of platelet function.

2. Paracetamol

It is commonly administered for the short-term treatment of mild to moderate pain and febrile critically ill patients with infection. It differs from the available opioids and NSAIDs, since paracetamol does not increase the incidence of nausea, vomiting and respiratory depression that can occur with opioids, or the platelet dysfunction, gastritis and renal toxicity that are associated with NSAIDs. It has a relatively good safety profile but there is limited information regarding IV use in critically ill patients. The study to date has described that paracetamol can cause transient abnormalities of liver function and may cause hypotension in critically ill patients. Acute liver failure is the most serious potential complication of the use of paracetamol. The key criteria for assessing potential hepatotoxicity with conventional doses of paracetamol may include hypoxic injury, altered pharmacokinetics, relative over-dosage, muscle glutathione depletion, malnutrition, dehydration, older age and alcoholism which are often seen in critically ill patients [176]

3. Prop-paracetamol

It is a prodrug form of paracetamol which is formed from the esterification of paracetamol and the carboxylic acid diethyl glycine. It has the advantage of making it more water-soluble. It is used in postoperative care and is delivered by intravenous route[177]

4. α2-agonists

The Clonidine and Dexmedetomidine are α2-adrenoceptor agonists, which provide both analgesia and sedation. Hence, they are also termed as analgosedation agents. Dexmedetomidine has eight times more affinity for α2-receptors compared with clonidine. Dexmedetomidine infusion has been shown to reduce the prevalence and duration of confusion and delirium when compared with the use of morphine and midazolam [175] α2-Agonists are used to improve the quality of analgesia and aid opioid rotation in opioid tolerant individuals. The side-effect profile of both α2-agonists includes bradycardia, cardiac asystole and hypotension. Although rare, it can cause rebound hypertension and can cause withdrawal syndrome.

5. Ketamine

It is an N-methyl-aspartate antagonist, commonly used as analgosedative agent. Its use in combination with the opioid PCA reduces the opioid consumption and side effects. In combination with midazolam, ketamine provides effective analgesia in sickle cell crisis patients. Ketamine has an opioid-sparing effect and commonly used in lower dosage in burns patients. The main side effects of ketamine are tachycardia, hallucination, delirium ketotonia and increase intracranial pressure [175]

6. Magnesium

It acts through the NMDA receptors and acts as adjunct by reducing analgesic requirements without any major adverse effects, but there is no evidence that magnesium has any opioidsparing effects in the critically ill patients [175]

7. Gabapentinoids

The Gabapentin and Pregabalin work by binding to the α2δ subunits of voltage-dependent calcium ion channels. They reduce the development of hyperalgesia and central sensitization and are useful adjuncts in the treatment

of neuropathic pain. Gabapentin compared with Carbamazepine or placebo reduces pain intensity in patients with GBS (Gillian Barrie syndrome) without increasing side effects. Gabapentinoids are used mainly in neuropathic and post-burn debridement pain. The extra advantage is that these medications are available in the enteric form and get absorbed in the duodenum; hence, one has to be careful when the patient is fed through a jeujenostomy tube. The major side effects of these medications are confusion, dizziness, ataxia and convulsions [175]

❖ Mode of analgesia administration in ICU patients

The mode of analgesic medication administration is an important factor for the pharmacologic management of pain in the ICU. Intravenous (IV) administration is more commonly the route of choice in critically ill patients because of altered GI tract function that could lead to unpredictable absorption of medication. Intravenous route is generally preferred over subcutaneous or intramuscular routes given potentially inadequate absorption due to regional hypoperfusion due to shock, subcutaneous oedema. The Fentanyl patch can be used for chronic pain relief in stable patients but not in ICUs or for acute pain relief because of the 12–24 h delay in peak serum levels. The choice of intermittent versus continuous infusion administration depends on factors such as the frequency and severity of pain and the pharmacokinetics of the analgesic medication. The administration in bolus is associated with the variation in the peak plasma concentration, since the infusion maintains a more stable concentration but can lead to accumulation of medication in patients with renal or liver failure.

a. **Patient-controlled analgesia (PCA)**
It is an effective method for administering analgesic medication and gives patients a sense of control over their pain. Patients have autonomy on when and how much medication they receive. However, this technique requires awake and orientated patients which make use of PCA limited in ICU patients. In combination with intravenous paracetamol and proparacetamol, the opioid consumption is significantly less [177]

b. Nurse-controlled analgesia (NCA)
It is inferior to the PCA but still can be useful, as nurses can administer the analgesia quickly when required or during the procedures.

c. Regional (nerve blocks) and neuraxial (spinal or epidural)
Analgesia techniques are used in ICU-selected trauma patients and surgical procedures. Epidural analgesia is probably the most commonly used regional anesthetic technique in the ICU. It is more useful in critically ill postoperative thoracic, abdominal, major vascular surgery, orthopedic surgery and trauma patients. Positioning patients during catheter insertion is a challenge for using regional anesthesia in ICUs. The main disadvantages of epidural and regional analgesia are the rare but catastrophic complications such as infection, epidural hematoma formation and nerve damage, which can occur in ICU patients who have a high risk of developing these complications [176] The combination of intravenous opioid PCA, paracetamol and regional anesthesia techniques is multimodal analgesia which decreases the total opioid analgesia consumption and hence decreasing the side effects and better patient comfort. The NCA proved to not be superior to PCA and increases the rapid response team activation.

❖ Few final recommending points

1. Hospital pain team
Consider referring complex ICU patients to the hospital pain team. It helps the patients on multimodal therapy but if still experiencing severe pain. Referral to the pain team can often lead to an increased level of support that would benefit the suffering patients, and once patients are discharged from the critical care unit, the pain team follows them to the ward [178]

2. **Alternative therapy**
The alternative medicine modalities of pain management like transcutaneous electrical nerve stimulation (TENS), acupuncture and aromatherapy have a very weak evidence base pain management in intensive care, but should be considered as the adv erse-effect profile is low [175]

3. **Reassessment**
Patients must be evaluated hourly to ensure appropriate response to therapeutic interventions so that health-care providers can proactively act to relieve pain. If reassessment reveals inadequate pain control despite the initiation of therapeutic interventions, we should consider titration of medications, rotation of medications or changes in the route of administration [178]

4. Guidelines and protocols

These guidelines should be developed that combine a scientific basis and expert opinion.

Wellness model from the World Health Organization's treatment of pain after cardiac surgery, we can see that guidelines and protocols lead to the effective management of post-cardiac surgery pain. If we look at the complexity of ICU pain, we need to have organized protocols to help us care for these patients. The examination of published literature reviews and evidence based guidelines can facilitate the development of institution-specific guidelines.

5. Clinical pathways

It provides a consistent and repeatable time line for planning individualized patient care. The pathway details the precise course of the patient, including multidisciplinary elements. It includes history, examination, diagnostics and treatment and incorporates pre-emptive treatment for procedures as well as management of chronic pain issues [178]

6. Checklists

It is a way to verify that clinical pathways or tasks are completed and it is a good way to ensure that pathways or tasks are followed. It helps in errors prevention [178]

CURRENT PROSPECTS AND ADVANCEMENTS IN NEUROIMAGING OF PAIN

Newer areas of neuroimaging for chronic pain research involve identifying brain based biomarkers for prediction of who will develop pain after surgery, patient prognosis, and to aid in treatment selection for individual patients. Predictive signatures, or patterns of brain activity and structural differences, and clinical phenotypes of chronic pain are emerging through continued research in these areas. Eventually these brain signatures and clinical phenotypes may provide more specific predictive and prognostic measures to allow for improved risk assessment and advice (in particular for patients undergoing elective surgeries), as well as personalized treatment for unique chronic pain subgroups, possibly ultimately on an individual patient basis (for review:[179]). As one example of predictive research findings in progress, greater levels of correlated activity between the medial prefrontal cortex and the ventral striatum, a subcortical brain region involved in motivation and value processes, predicted worse outcomes (i.e., lower propensity for recovery) in patients with low back pain[180]. Thus, neuroimaging signatures may provide an additional data point to complement classic phenotypical predictors of outcome (e.g., age, sex, psychological status). A pain signature, distributed pattern of brain regions and specific activity levels within those regions, that is specific to acute heat pain sensitivity has been identified[6,181]. Such pain brain signatures may lead to enhanced predictive patterns of chronic pain patient subtypes in the future. In fact, researchers have recently identified a pain signature for pressure and multisensory sensitivity in fibromyalgia[182]. These studies and others[43,183] have used multivariate methods for analyzing neuroimaging data. Multivariate methods allow for the identification of these preliminary signature patterns of brain structure and function in patients with chronic pain. Researchers are currently using multivariate methods operating on the premise that these methods are statistically better suited to identify patterns from neuroimaging data sets which contain approximately 200,000 voxels (3 dimensional pixels) per subject. Furthermore, multivariate methods provide output measures of classification accuracy, sensitivity, specificity, negative and positive predictive value. One major caveat, however, is that analyses using multivariate methods, similar to most neuroimaging analyses, still require groups of chronic pain patients and healthy volunteers for comparison. Further, acute pain and chronic pain signatures from these analyses are currently in the very preliminary research phase, are largely exploratory, and the signature patterns identified will require numerous iterations of improvement and validation prior to any glimpse of practical and reliable clinical application. Critically important medico-legal concerns surrounding the topic of brain biomarkers for chronic pain have been recently described in excellent detail in another review article[184].

Other advancements in the field of pain neuroimaging include the use of combined neuroimaging modalities, large-scale multi-site investigations, meta-analytic research, and spinal cord fMRI. Neuroimaging researchers are now more frequently using analysis methods that combine neuroimaging modalities to understand chronic pain. One such investigation has recently used combined PET imaging and fMRI to identify reduced μ-opioid receptor availability and decreased pain-evoked BOLD activity in antinociceptive regions, such as the dorsolateral prefrontal cortex and anterior cingulate cortex, in individuals with fibromyalgia[185]. Neuroimaging of pain is also being included as a major component of large-scale multi-site investigations focused on understanding idiopathic chronic pain conditions such as urological chronic pelvic pain (i.e., interstitial cystitis, chronic prostatitis, bladder pain syndrome)[186]. Such neuroimaging investigations have identified changes among chronic pelvic pain patient data, collected and analyzed across multiple sites, that indicate dysfunctional resting state default mode connectivity[71], increased gray matter density within the pelvic somatosensory cortex[43,44], increased functional connectivity of the pelvic motor cortex to the posterior insula, a

region involved in processing intensity or salience of pain[74], and changes in white matter axon diffusivity[57]. These types of collaborative multi-site investigations are also allowing for longitudinal investigations that have shown changes in brain activity that track symptom profiles (improved and worsening symptoms) over time[187]. Meta-analyses of neuroimaging data are another useful tool becoming more prominently used to collectively re-analyze neuroimaging data from multiple previously published neuroimaging investigations (e.g.,[188]). Meta-analytic studies are beneficial for identifying the most reproducible, and therefore more reliable, results from neuroimaging analyses of chronic pain populations. For example, one meta-analysis has determined that brain regions, including dorsal anterior cingulate cortex, anterior insular cortex and dorsal medial thalamus, are commonly activated during tasks related to pain perception, innocuous stimulation, emotion, memory and introspection across multiple studies, suggesting that these brain regions are responsible for the processing and integration of salient information[132]. Spinal cord imaging is emerging, as field of neuroimaging research complimentary to brain and brainstem imaging, due to technological advancements in fMRI data collection and analysis[187–189]. Recent early investigations in spinal cord fMRI have provided additional evidence of descending modulatory control of pain[190-191], as well as changes in spinal cord and brainstem activity in healthy humans after central sensitization[36], and in individuals with chronic pain[192]. These findings are generally complementary to results from brain neuroimaging research, specifically, with greater stimulus-induced activation within the spinal cord being correlated with increased pain sensitivity. Ultimately, further advancements in these areas of promise, and others, will continue to contribute to the wealth of knowledge gained thus far by the neuroimaging of pain in healthy and clinical states.

FUTURE TREATEMENT

- Neuroimaging has advanced our understanding of chronic pain and has collectively provided a framework for patient-clinician conversation regarding the complex, biopsychosocial aspect of chronic pain and the importance of multi-modal therapy for its alleviation.
- Neuroimaging research has demonstrated definitive involvement of the central nervous system in the development, maintenance, and experience of chronic pain.
- Structural and functional neuroimaging has helped elucidate central nervous system contributors to chronic pain in humans.
- Neuroimaging of pain has provided a tool for increasing our understanding of how pharmacological and psychological therapies improve chronic pain.
- To date, findings from neuroimaging pain research have benefitted clinical practice by providing clinicians with an educational framework to discuss the biopsychosocial nature of pain with patients.
- Future advances in neuroimaging-based therapeutics (e.g. transcranial magnetic stimulation, real-time functional magnetic resonance imaging neurofeedback) may provide additional benefits for clinical practice.
- In the future, with standardization and validation, brain imaging could provide objective biomarkers of chronic pain, and guide treatment for personalized pain management. Similarly, brain based biomarkers may provide an additional predictor of perioperative prognoses.

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