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Surgically-Induced Neuropathic Pain (SNPP): Understanding the Perioperative Process

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Abstract

Objective—Nerve damage takes place during surgery. As a consequence, significant numbers (10–40%) of patients experience chronic neuropathic pain termed surgically induced neuropathic pain (SNPP).

Background—The initiating surgery and nerve damage set off a cascade of events that includes both pain and an inflammatory response, resulting in '*peripheral' and 'central sensitization'*, with the latter resulting from repeated barrages of neural activity from nociceptors. In affected patients these initial events produce chemical, structural and functional changes in the peripheral (PNS) and central nervous (CNS) systems. The maladaptive changes in damaged nerves lead to peripheral manifestations of the neuropathic state – allodynia, sensory loss, shooting pains etc., that can manifest long after the effects of the surgical injury have resolved. The CNS manifestations that occur are termed '*centralization of pain*' and affect sensory, emotional and other (e.g., cognitive) systems as well as contributing to some of the manifestations of the chronic pain syndrome (e.g., depression).

Conclusions—Currently there are no objective measures of pain in the peri-operative period. As such intermittent pain or continuous may take place during and after surgery. New technologies including direct measures of specific brain function of nociception and new insights into preoperative evaluation of patients including genetic predisposition appear to provide initial opportunities for decreasing the burden of SNPP until treatments with high efficacy and low side effects that either prevent or treat pain are discovered.

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Introduction

Surgically-Induced Neuropathic Pain (SNPP) is a significant clinical problem, with *p*ersistent pain estimated to occur in 10–50% of individuals after common operations (Kehlet et al., 2006). Postsurgical neuropathies may be a consequence of transection, contusion, stretching, or inflammation of the nerve (Staff et al., 2010), and is the only neuropathic pain syndrome that is fully under our control. SNPP is reported to occur in 60% of patients after limb amputation (Manchikanti and Singh, 2004), in 20–40% after mastectomy (Stevens et al., 1995; Smith et al., 1999; Vilholm et al., 2008), in 20–40% after thoracotomy (Steegers et al., 2008; Guastella et al., 2011), and in 20% after hernia repair (Massaron et al., 2007). In 2006, an estimated 53.3 million surgical and nonsurgical procedures were performed during 34.7 million ambulatory surgery visits (Cullen, 2009), while in 2007 approximately 45 million inpatient surgeries were performed (Hall MJ, 2010). It should be noted that while the majority of post-surgical pain is considered to be neuropathic, in many of these studies the clinical pain phenotype (i.e., neuropathic pain) was not specifically measured using quantitative sensory testing. The nature of the surgical insult has a variable influence on the incidence of chronic neuropathic pain (reviewed in (Perkins and Kehlet, 2000), and although a preexisting painful condition may influence the predisposition to SNPP pain (Gerbershagen et al., 2009), the issue seems to be a consistent one: surgical trauma commonly results in neuropathic pain. Severity varies from no or minimal pain to significant pain (> 4/10 on a Visual Analogue Scale), with severe pain reported in 2–10% of patients (Kehlet et al., 2006). Thus, SNPP is epidemic, and even by conservative estimates, the number of patients suffering from neuropathic pain is significant. SNPP results in prolonged suffering, and the burden to the individual and society are enormous (Shipton and Tait, 2005; VanDenKerkhof et al., 2006; Haller et al., 2011) (O'Connor, 2009).

This review is presented in 4 sections: (1) *The Surgical Patient and SNPP* – damage to peripheral nerve and pain are critical elements that may occur on a background of genetic, gender, previous or ongoing pain, and epigenetic factors. While the issue of SNPP is a problem, there are medical process that may exacerbate the issue; (2) *The Incision – Consequences Beyond Initial Nerve Injury* – although some nerve damage is unavoidable, a cascade of events may occur that includes alterations in peripheral nerves, 'central sensitization' and changes in brain systems referred to as 'centralization of pain' in which there alterations not only in sensory but also emotional, cognitive and other neural circuits and brain structure. (3) *The Current Clinical Conundrum of SNPP and Need for Objective Measures of Nociception and Pain* – considering the surgical insult as the proximal event, SNPP can be fairly described as chronic, frequently neither observed nor treated by those present during the surgery. Robust and objective measures of nociception and pain are necessary as advances in prevention and management of SNPP may only be achieved by what can be observed, defined and understood. (5) *Decreasing the Risk of SNPP* - doing better now with current information until more effective treatments are hopefully available. Figure 1 summarizes the issues reported in this paper.

1. The Surgical Patient and SNPP

Most surgical procedures are performed on an elective basis, thereby allowing time to prepare patients for the event and post- surgical treatments. According to Katz and Seltzer surgery, unlike other injuries, presents a unique set of circumstances in which the precise timing of the physical insult and ensuing pain are known in advance (Katz and Seltzer, 2009). A comprehensive pre-operative assessment and anesthetic plan, including perioperative pain control, is performed for all patients scheduled for surgical procedures. As the type of surgery and coexisting medical processes may influence the occurrence of

SNPP, it is important to elevate these issues in the awareness and thinking of practitioners during anesthetic and surgical planning. According to Raja and Jensen, a better understanding of the predictors of postsurgical pain will help identify those patients who are likely to need additional care for optimization of perioperative pain management (Raja and Jensen, 2010). Thus, the opportunity to evaluate those most likely to be affected by the surgery perhaps should have the same importance as other clinical evaluative processes that may be considered to be routine in the post-surgical considerations (e.g., rehabilitation, immediate pain control etc.).

1.1. Delayed Processes vs. Immediacy of Surgery

In the perioperative period, the focus naturally falls on the immediate severity of the surgical condition being treated rather than on the long-term consequences; this is true both for the patient and the healthcare providers. In this context, the consequence of the procedure, namely chronic pain, seems relatively inconsequential compared with the significant clinical condition and surgical treatment. The issue is further complicated by two problems: (i) Lack of immediacy of the problem of SNPP since it may frequently have a delayed onset of months to years (Schott, 2001); and (ii) the current model of discontinuous medical care commonly seen in the United States. The patient is an intermittent partner with multiple medical specialties – primary care, surgery and anesthesia, and then return to primary care once surgical follow-up is complete. Thus, the translation of awareness of the problem (SNPP) to active responsibility for continued care (primary care physician) is distant from those who are close to the inciting event (surgeon, anesthesiologist, hospitalist). However, as medicine has markedly advanced in reducing anesthetic and surgical mortality, secondary issues (such as pain control and intraoperative awareness) are becoming more salient. In a medical model, these would be considered co-morbid risk factors.

1.2. Prevention of SNPP

A number of approaches have been attempted to prevent SNPP, most notable of which is "*pre-emptive analgesia*" (Dahl and Moiniche, 2004; Dahl and Kehlet, 2011). Although preclinical studies were very promising (Woolf and Chong, 1993), clinical studies have not provided consistent results (Pogatzki-Zahn and Zahn, 2006). Many such studies only evaluated the immediate postoperative effects such as analgesic consumption (Katz and McCartney, 2002; Ong et al., 2005). A second approach is the use of multimodal techniques that block nociceptive pathways at different levels (viz., peripheral and/or axial) or by different mechanisms (viz., opioids and/or local anesthetics) (Grape and Tramer, 2007). As with pre-emptive analgesia, few approaches across multiple controlled trials have been shown to be highly effective. More recent data with continuous neural blockade would suggest that some approaches provide better outcomes (Karanikolas et al., 2011). Although control of post-surgical neuropathic pain has received more attention, it is unclear whether this has a major impact on long-term clinical outcome once a process of 'central sensitization' and 'centralization of pain' (see below) has been initiated.

1.3. Pre-morbid Factors

There is marked patient variability in the response to identical surgical procedures, so that not all surgical procedures and nerve injury lead to a neuropathic pain state. A number of factors pertaining to the individual patient may increase the risk of SNPP and include age, gender, genetics, preexisting pain, and behavior.

Age and Gender—Adult neural systems are less adaptive (Cusick, 1996) and more likely to give rise to chronic pain. Indeed, neuropathic pain is relatively uncommon in children (Walco et al., 2010). However, surgical events at an early age may have long-lasting

consequences on subsequent sensitivity to pain (Taddio et al., 1995) (Aasvang and Kehlet, 2007; Kristensen et al., 2010), although the risk of developing chronic pain after groin hernia repair or thoracotomy is lower if the surgery is performed at a young age (Aasvang and Kehlet, 2007; Kristensen et al., 2010). Although women have a greater incidence of pain conditions, including neuropathic pain (Wiesenfeld-Hallin, 2005), little information is available on the incidence of SNPP and gender. In a recent study evaluating effect of patient sex on general anesthesia and recovery, women emerged more quickly from general anesthesia but their overall quality of recovery was poorer and pain scores were higher (Buchanan et al., 2011).*Genetic Polymorphisms:* Genetic studies in preclinical models have shown that neuropathic pain variance is heritable. Clinical examples include the potassium channel alpha subunit KCNS1, involved in neuronal excitability (Costigan et al., 2010), and the haplotype of the GTP Cyclohydrolase 1 (GCH1) gene that is associated with less pain following discectomy for persistent radicular low back pain (Tegeder et al., 2006). Thus, screening for genetic polymorphisms could help define those individuals prone to a transition to persistent pain.

Pre-surgical Pain—The presence of preoperative pain, regardless of the relationship to surgical site, significantly increases the risk of developing SNPP (Gerbershagen et al., 2009; Gerbershagen et al., 2010; Ozgur et al., 2011).

Behavior—The importance of understanding the effects of a patient's psychological state prior to surgery is gaining increased attention (Rosenberger et al., 2006; Celestin et al., 2009). For example, *attentional avoidance* of negative experiences prior to surgery proved to be a powerful predictor (as defined by decreased analgesic use) of acute postoperative pain (Lautenbacher et al., 2011),outperforming predictors such as depression, anxiety, or pain catastrophizing (Granot and Ferber, 2005; Hinrichs-Rocker et al., 2009; Papaioannou et al., 2009). High catastrophizing is associated with greater levels of acute postoperative and chronic pain (Pavlin et al., 2005; Khan et al., 2011). The role of these predictors in SNPP remains unclear, although increased postoperative pain intensity may be a predictor of chronic pain (Nikolajsen et al., 1997b; Hanley et al., 2007).

2. "The Incision" – Biological Consequences Beyond Initial Nerve Injury

While there are clearly susceptible nerves that are potential targets of surgical trauma (viz., genito-femoral, iliohypogastric, ilioinguinal, femoral, sciatic, intercostobrachial, intervertebral) (Dobrogowski et al., 2008), any region of the body is susceptible because of the nature of tissue innervation. Following unavoidable nerve damage, a cascade of events can occur (summarized in Figure 1) that comprises alterations not only in peripheral nerves but also in brain systems. These changes may include enhanced sensitivity in nociceptive (nociception is defined as "*The neural process of encoding noxious stimuli*" (www.iasp-pain.org)) pain pathways and 'centralization' of pain (defined in detail below).

This phenomenon can be illustrated by surgical treatment of inguinal hernia repair, a common and seemingly straightforward procedure usually performed in a relatively young and healthy population. Chronic post-herniorrhaphy pain is reported in 30–50% of patients (Loos et al., 2007; Massaron et al., 2007) (Poobalan et al., 2003; Leslie et al., 2010), and even operations performed in childhood (when neural systems are apparently more adaptive or plastic) are associated with moderate to severe pain in 2% of patients (Aasvang and Kehlet, 2007). Nerve damage may be present without pain, as sensory dysfunction is common and includes hypoesthesia and hyperalgesia to quantitative sensory testing and pressure (Mikkelsen et al., 2004; Aasvang and Kehlet, 2010). Numbness is also reported to occur in association with pain (Loos et al., 2007). It is unclear if the changes relate to nerve injury during surgery and/or from inflammatory responses to the surgical mesh. Technical

advances in the surgical approach may reduce the incidence of chronic neuropathic pain following inguinal hernia repair (Kumar et al., 2002).

The pathophysiology of post-surgical pain has been reviewed elsewhere (Kehlet et al., 2006; Costigan et al., 2009; Costigan et al., 2010). Briefly, *nociceptive pain* results from activation of high threshold peripheral sensory neurons (nociceptors), as caused by incision, and diminishes once the peripheral driving force is removed. *Inflammatory pain* is increased pain sensitivity due to inflammatory mediators lowering the threshold of nociceptors that innervate the damaged and inflamed tissue; it is also associated with exaggerated responses to normal sensory inputs and persists until the wound is healed and the inflammation resolves. *Neuropathic pain* is due to nerve injury and is characterized by sensory loss with paradoxical hypersensitivity (Kehlet et al., 2006).

Pain has a more complex definition than nociception. While nociception may be defined as the sensation relating to activity induced in the nociceptor and nociceptive pathways and specifically, pain that arises from actual or threatened damage to non-neural tissue (i.e., neural process of encoding noxious stimuli), pain is defined as "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*" (Mersky and Bogduk, 1994). Pain perception, a subjective experience, requires cortical function. During anesthesia, nociceptive signals may still be present activating well-described afferent pathways to multiple brain areas including sensory, emotional, autonomic and modulatory. Pain may be perceived if the patient is inadequately anesthetized. The transformation of nociception into pain, and acute pain into chronic pain is complex and difficult to define (Katz and Seltzer, 2009) (see below), but once a nerve is injured an ongoing process unfolds that may be modulated but not easily reversed by current treatments. Even with improved post-operative pain management (Powell et al., 2009), intermittent (breakthrough) pain can still become a chronic syndrome.

2.1. Activation of Nociceptors and Direct Nerve Injury – 'Blasting' the Central Nervous System

Activation of nociceptors by noxious stimuli and direct injury to nerves results in a barrage of afferent fiber activity (Sivilotti et al., 1993). Nerve injury is a prerequisite for chronic postsurgical pain and is associated with a cascade of events at the chemical, structural and functional levels (Goff et al., 1998; Zimmermann, 2001; Scholz and Woolf, 2007; Costigan et al., 2009). Nerve injury can result in spontaneous firing in C-fibers (Wu et al., 2001) or degeneration of myelinated fibers (Wu et al., 2002), processes which can induce a phenotypic switch (Neumann et al., 1996) and central sensitization (see below). Injured nociceptive neurons become sensitized (activated at a lower threshold) and may show activity in the absence of any stimulation (Bove and Dilley, 2010) or as a result of the inflammatory reaction to tissue injury (Xiao and Bennett, 2007). Following nerve damage, adaptive processes are induced that try to repair the damage: these include those from the nerve itself (e.g., neuronal sprouting) or elements from the surrounding milieu (e.g., anti-inflammatory molecules). A phenomenon that is becoming increasingly appreciated is 'muscular neuropathic pain' in that damage to muscle produces a syndrome akin to neuropathic pain (Alvarez et al., 2011). In animal experiments muscle damage contributes to central sensitization (Vernon et al., 2009 19748401), and attempts to diminish muscle pain are being studied (Rubino et al., 2010).

Consequently, if adequate analgesia is not provided both intra- and postoperatively, abnormal nociceptive drive continues unabated. As noted by Patrick Wall, the nociceptive drive following nerve damage that is translated into spontaneous after nerve injury may occur soon after the insult or after a substantial delay (Wall, 1991). Figure 2 offers a categorization of nociception or pain as a result of the surgical insult or manipulation (Type

1), anesthetic wear-off (Type 2) and inadequate analgesia during or post-operatively (Type 3). Figure 3 summarizes pain or nociceptive processes across the perioperative period.

2.2. Igniting the Brain - Central Sensitization of Nociceptive Systems

"Nociceptor inputs can trigger a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, the phenomenon of central sensitization" (Woolf, 2011). As reviewed by Kehlet et al., central sensitization amplifies nociceptive and pain signaling and is characterized by an abnormal perceptual response to normal sensory input as well as the spread of sensitivity beyond the peripheral site of injury (Kehlet et al., 2006). Surgery thus produces alterations in nociceptive inputs from the time of incision and such inputs may change nociceptive processing in various spinal cord and brain circuits including neuronal connectivity (Seifert and Maihofner, 2011). A pre-surgical chronic pain condition is believed to have sensitized the brain and may exaggerate this process. Brain regions found to be activated by C-fiber evoked responses of dorsal horn neurons include the contralateral thalamus, primary and secondary somatosensory cortex S 1 and S2), anterior and posterior insula, mid-anterior cingulate cortex (ACC), and supplemental motor areas (SMA) (Staud et al., 2007). This study suggests that C-fiber 'barrage' affects not only regions primarily involved in sensory nociceptive and pain processing (S1, thalamus, and posterior insula) but also regions involved in emotional processing of pain (cingulate cortex, insula, periaqueductal grey), pain modulation (ACC), pre-motor activity (SMA, cerebellum) and cognition (ACC, prefrontal cortex). Following on from the difference between nociception and pain as presented earlier, pain perception may be understood as a result of transformation of nociceptive representation into subjective magnitude assessment within the insula of the brain (Baliki et al., 2009). Given that the insula is important in interoceptive (evaluation of stimuli originating within the body) processing, the notion that such regions play a role in this may be targets for future diagnosis and treatments.

2.3. Altered Brain States – Centralization of Pain

Brain systems are modulated by disease states and the process of central sensitization, usually reserved in the pain dialogue for effects that enhance sensitivity in pain pathways, now needs to include sensory, emotional and modulatory pathways. In patients with chronic pain, all these systems are maladaptive and the term 'centralization of pain' should be applied. The use of the term centralization represents an ongoing cascade of changes in brain circuits as a result of pain. Centralization may produce changes that confer the evolution of new behaviors as a result of the ongoing pain (e.g., increased pain sensitivity/responses, depression or altered cognition). It is considered a plastic process that may be reversible or modifiable either by altering the brain state and consequently structure or function (e.g., peripheral nerve blocks may reverse "cortical organization" (Birbaumer et al., 1997 9204932) but these approaches have not shown long-term effects in chronic pain. Thus, the concept refers to brain changes that are initially driven by nociceptive signals or de-novo brain-specific pain conditions (e.g., central pain due to thalamic stroke) but as a result brain function becomes abnormal or maladaptive. Perhaps a better way of defining centralization of pain would be "pain-induced changes in brain circuits resulting in altered/pathological behaviors". Such changes have been termed maladaptive plasticity (with an emphasis on cortical aspects) by others (Flor et al., 2006 17053811).

As discussed above, the pre-operative condition of a patient is a critical component in the potential to adapt to the perioperative stress. Patients with certain genetic traits, sensory (pain, increased pain sensitivity) or behavioral abnormalities (e.g., depression, anxiety, catastrophizing) may be more predisposed to developing chronic neuropathic pain (Hinrichs-Rocker et al., 2009; Dimova and Lautenbacher, 2010) (Gerbershagen et al., 2009;

Ozgur et al., 2011). Non-pain systems may also be altered, notably in patients with conditions such as depression or anxiety. Following acute or chronic pain, a negative affective state is common in human and animal models (Hummel et al., 2008; McKenzie et al., 2010). Nerve injury can also contribute to therapeutic resistance as shown by decreased pharmacological sensitivity of dorsal root ganglion neurons to morphine or lidocaine analgesia (Kolesnikov et al., 2007). The degree of nerve damage may correlate with the development of SNPP, but studies to support this contention are still lacking.

2.4. Long-term consequences of SNPP

As with all chronic pain conditions, SNPP may alter brain systems (Tracey and Mantyh, 2007; Maihofner et al., 2010; Apkarian et al., 2011; Peyron and Faillenot, 2011) and recent imaging studies have contributed to our understanding of changes in central neural networks in neuropathic pain (Maihofner et al., 2010). The chronic neuropathic pain state is characterized by functional (Becerra et al., 2006; Geha et al., 2008; Cauda et al., 2010), morphometric (Apkarian et al., 2004; DaSilva et al., 2008) and chemical (Harris et al., 2008) changes. Functional magnetic resonance imaging (fMRI) provides insights into the progressive plasticity of neural networks, and recent data indicates that reversal of these changes, at least as assessed by morphometric measures of gray matter, provide markers for the disease state and effects of therapy (Borsook et al., 2011). In addition to those changes noted above, there are alterations in endogenous anti-nociceptive systems that seem to either enhance pain (pain facilitation) or decrease their normal inhibitory effects. Apart from the well-known endogenous modulatory systems (Basbaum and Fields, 1984), relatively little information is available on the endogenous anti-nociceptive molecules or processes. There is some evidence that pro- and anti-inflammatory cytokines may significantly influence responses of damaged or functionally altered neurons (Moalem and Tracey, 2006; Abbadie et al., 2009). Insights into new molecules such as resolvins (Price, 2010), that are involved in inflammatory pain, may find new applications in preventive processes including the development of maladaptive neuropathic states.

3. The Current Clinical Conundrum of SNPP and Need for Objective Measures of Pain

The challenges to prevention and management of SNPP relate to the timing of the initiating surgical insult and the definition of SNNP, the current model of medical care, and the evaluation of nociception with a critical need for objective measures of nociception that may be the harbinger of the later evolution of pain. Every time an individual undergoes surgery, the chances of having a post-operative chronic nerve pain syndrome is approximately 30%, ranging up to 50% in some common surgeries such as hernia repair (Poobalan et al., 2003; Leslie et al., 2010). The burden to the individual and society are enormous (Shipton and Tait, 2005; VanDenKerkhof et al., 2006; Haller et al., 2011).

3.1. The Beginning of SNPP – Ill Defined

By definition, chronic pain is ‘pain lasting for more than 3 months’. This is somewhat of an arbitrary notion that provides a temporal index but not a useful biological or mechanistic index. Some patients develop SNPP almost immediately after injury, while in others it is only observed weeks or months after the injury. Thus the notion that a period of time should be the arbiter of a definition of SNPP is problematic when SNPP likely arises from surgery – most often a premeditated, defined intervention that damages nerves at the outset (Millan, 1999; Schaible, 2007; Voscopoulos and Lema, 2010; Woolf, 2011). If SNPP is considered a neuropathic pain condition at the time of the surgical insult (induced by nociceptive processes), and because most surgeries are performed on a non-emergent bases, then time and measures to evaluate attacks on the central nervous system by afferent nociceptive drive

and nerve damage would become paramount. Without robust and objective measure of nociception during and after surgery, utilizing subjective assessments or waiting for patients to request or self-administer medication (including patient controlled analgesia) allows for gaps in continuity of full and complete pain control in the perioperative period.

3.2. Lack of a Continuum of Care

As discussed above, surgeons assume primary responsibility for care of patients and early post-surgical follow-up, with care subsequently reverting to the patient's primary provider. During the perioperative period, anesthesiologists assume much of the responsibility for pain control but are rarely provide follow-up with patients. As the development of neuropathic pain may occur weeks to months after the surgery, implementation of a coordinated continuum of care may provide for improved outcomes (Counsell et al., 1994).

3.3. Evaluation of Pain

Current evaluation of pain in the perioperative period is based on subjective and indirect physiologic measures (Van der Vleuten et al., 1991; Pies, 2007). However, robust and objective measures of pain are necessary to detect and prevent repeated nociceptive afferent discharges, central sensitization, and alterations in brain systems. Advances in prevention and management of post-surgical pain may only be achieved by what can be observed, defined and understood. Pain following trauma perhaps can be considered akin to water flow in that if there are any gaps in analgesic coverage, pain will 'flow' from its site of injury. Without proper measurement it is not possible to determine the frequency and magnitude of perioperative pain.

Complete Nociceptive Afferent Blockade—Ideally, no nociceptive afferent information will pass along the nerve in the perioperative and post-operative period and so prevent central sensitization. However, nociceptive information may still be ascending from the surgical site to the brain with even a minimal or transient break in analgesia during anesthesia and/or postoperatively, when nociceptive pain is likely to be most intense. Animal imaging data support this notion as activation of primary sensory brain systems can be observed during anesthesia (for a review see Borsook et al., 2010).

Pain and Consciousness—Although subconscious processing of pain cannot be defined by most patients, it is likely that intraoperative awareness is an indicator of inadequate treatment of pain (Tinnin, 1994). As the incidence of awareness varies from 0.1% (Leslie and Davidson, 2010) to 0.6–0.8% (Blusse van Oud-Alblas et al., 2009; Malviya et al., 2009), intraoperative pain is likely to be occurring in a meaningful number of patients.

Efficacy of Anesthetic-blockade of Pain Transmission – 'On Knowing' in the OR—How do we know that an anesthetic is effective in completely blocking nociceptive transmission to the central nervous system? Intraoperative EEG recordings have a low correlation to clinical signs of changes in the anesthetic state (Bischoff et al., 1998). Data suggest increased nociceptive signal transmission that is not blunted by isoflurane-nitrous oxide anesthesia. During incision and periosteal manipulation, surgical stimulation resulted in significant increases in the N20 and P25 amplitudes of the somatosensory-evoked potentials (SSEPs) in the contralateral somatosensory cortex, and was not associated with autonomic responses (Rundshagen et al., 1997). Similar data is observed in animals under anesthesia in which pain stimuli produce activations in the somatosensory cortex and other brain regions (see (Borsook and Becerra, 2011b) for a review). Late SSEPs in response to painful stimuli change under general anesthesia with different analgesic levels (Kochs et al., 1990). Anesthetics such as ketamine do not block SSEPS in primates (Ghaly et al., 2001). SSEPS are decreased but not abolished by epidural local anesthetics (Chabal et al., 1988).

Despite clinically effective blockade during spinal anesthesia with bupivacaine 0.5%, nerve potentials after nociceptive stimulation within the area of sensory block were often able to pass to the cerebral cortex albeit with a decreased amplitude and increased latency (Lund et al., 1987). In contrast, subarachnoid administration of lidocaine completely abolished SSEPs and cortical motor evoked responses (CMER), while meperidine or fentanyl did not completely abolish SSEP's (Fernandez-Galinski et al., 1996). Such findings can be interpreted as nociceptive information accessing the CNS as a result of surgical manipulation.

Regional Anesthesia and SNPP—Although patients may be able to communicate pain during regional anesthesia, the level of sedation may preclude this. As discussed in the preceding paragraph, nociceptive transmission may still occur in the presence of clinically adequate neural blockade. Regional anesthesia can be associated with nerve injury (Sorenson, 2008; Borgeat and Aguirre, 2011). Mechanisms include direct needle injury, local anesthetic toxicity (particularly intraneural injection), and compression from tourniquets (Hogan, 2008). Activation in nociceptive neurons was seen during nerve damage (nerve constriction) in both untreated rats and in rats receiving local anesthetic prior to the procedure; post-injury application of local anesthetic blocked the nociceptive activity (Sotgiu et al., 1994). A question is whether application of local anesthetic to the nerve following nerve injury will prevent activation of nociceptive neurons in humans? There is some evidence to support this notion. Although pre-emptive perineural injections of local anesthesia may not prevent phantom limb pain after amputation (implying that the afferent barrage that takes place with nerve damage activates pain systems)(Nikolajsen et al., 1997a; Wilson et al., 2008), more recent evidence indicates that post-operative continuous nerve blockade may provide long-term benefits (Schley et al., 2007; Borghi et al., 2010; Ilfeld, 2011). Other examples include studies that report that continuous postoperative infusion of local anesthetics perineurally or epidurally reduce chronic pain after ankle surgery (Blumenthal et al., 2011 21169609) and phantom pain after amputation (Karanikolas et al., 2011 21368651).

4. Decreasing the Risk of SNPP

Hopefully specific therapies that can either prevent or treat SNPP will become available in the future, especially as the current treatment efficacy is only around 30% (Backonja et al., 1998; Rowbotham et al., 1998; Wernicke et al., 2006). Until that time, the following strategies can be implemented.

4.1. Preoperative (Presurgical) Measures

It is fundamental that perioperative care between primary and specialist care be much better integrated. As SNPP may occur beyond the early perioperative period, patient education regarding the possible development of this condition is essential, and that the availability and need for specialized care be emphasized. Patients at higher risk for SNPP may be identified preoperatively by premorbid factors such as age (adult), gender (female), genetic polymorphisms (screening), preexisting pain, and behavior (depression, anxiety, catastrophizing). Assessment of these factors should become routine as part of the preoperative anesthetic and surgical evaluation.

4.2. Intraoperative Measures

Mitigating Peripheral Nerve Damage—Although any tissue is susceptible because of the nature of innervation, surgical damage to nerves can be mitigated by developing approaches that avoid damage to large nerve bundles. The size of the nerve lesion, in general, correlates with the likelihood of producing chronic neuropathic pain. New

approaches may be considered based on the findings in animal models. An example is limitation of the inflammatory response by the local injection of corticosteroid (Li et al., 2011), or the use of transcranial magnetic stimulation to inhibit nociceptive transmission (Leo and Latif, 2007). Surgery induces inflammation – cellular responses around the wound (Thacker et al., 2007) and if pain signals reach the CNS, changes in glial and other cells involved in neuroinflammation (Myers et al., 2006; Saab et al., 2008; Flierl et al., 2009). In addition the use of anesthetics such as ketamine – a drug that has profound anitinflammatory effects (Loix et al., 2011), may help diminish surgical and postsurgical inflrammation when used during surgery (Welters et al., 2011), and as in the case with PTSD (McGhee et al., 2008), may limit chronic pain as has been shown in other pain studies (Correll et al., 2004; Sigtermans et al., 2009). Other such drugs that may inhibit inflammation include minocycline (Pabreja et al., 2011) as well as other drugs currently in development.

Continuous Analgesic Blockade (CAB) and Measurement of Pain—How can we provide continuous analgesic blockade to diminish 'central sensitization' and 'centralization of pain' without objective measures of pain? Some new approaches have leveraged recent advances in brain imaging to develop systems that can monitor nociceptive signals in awake, sedated and anesthetized subjects (Becerra et al., 2009; Borsook et al., 2010). Such systems would allow for an objective and accurate measure of pain, thereby allowing the physician to optimize the dosage of sedative and analgesic drugs for each patient (Borsook et al., 2010). Near Infrared Spectroscopy (NIRS) has been found to reproduce known fMRI activations in humans in response to pain (Borsook and Becerra, 2011a), but unlike fMRI is more easily adaptable to the clinical situation. NIRS is used for non-invasive assessment of brain function by detecting changes in blood hemoglobin concentrations associated with neural activity. The potential use of this technology to measure pain responses in neonates was demonstrated with use of a commercially available system (Bartocci et al., 2006; Slater et al., 2006). Regardless of methodologies developed, the implementation of objective methods for pain measures in the intra- and post-operative period will be a major step in defining the magnitude of the problem. Ideally, such systems should be able to objectively define both awareness and pain such that multimodal output from different functionally specific cortical regions would provide a basis for more objective-based administration of anesthetic and analgesic agents (Figure 4).

4.3. Post-operative Measures

Patient Education—As for pre-operative measures, and because SNPP may be present soon after surgery and under diagnosed (Gray, 2008), manifestations of SNPP should be discussed with patients. Symptoms include spontaneous pain that may be burning or aching in nature, paroxysms of shooting pain, and even sensory loss. The majority of studies indicate that providing this information to patients may result in a decreased level of SNPP intensity (Stevens et al., 1995; Smith et al., 1999). Currently, patients with chronic pain generally delay seeking specialist pain care for months to years. Indeed, the American Pain Society notes that almost 40% of chronic pain sufferers are not currently going to a doctor for relief of their pain and most delay visiting a physician because they think they can handle the issue themselves (1999). There are ethnic, gender and other cultural differences that delay getting specialist pain care (McCracken et al., 2001; Rahim-Williams et al., 2007; Ben-Shlomo et al., 2008). Additionally, delays may also be a result of limited access to pain specialists in some countries (Lynch et al., 2007) and that waiting for treatment may have an effect on outcomes (Lynch et al., 2008).

While recent neuroimaging research has indicated changes in cortical volume in response to chronic pain (see (May, 2011) for a review), reversal or normalization of these changes may be observed when the pain is treated. From a surgical perspective, this has been

demonstrated in patients prior to and following hip repair (Rodriguez-Raecke et al., 2009; Gwilym et al., 2010) and more recently in other conditions using non-surgical approaches in chronic back pain (Seminowicz et al., 2011).

Treatment Approaches—Unfortunately, treatments for neuropathic pain are not highly effective. Placebo-controlled trials in neuropathic pain suggest approximately 30% efficacy, even for the two most commonly used agents (gabapentin, duloxetine) (Backonja et al., 1998; Rowbotham et al., 1998; Wernicke et al., 2006). Some treatments, such as opioids, may in fact produce changes in the brain (Upadhyay et al., 2010) and aggravate the neuropathic pain condition with increased hyperalgesia (Bannister and Dickenson, 2010; Martin, 2011). The use of opioids for treatment of chronic pain is now being tempered by a lack of efficacy, side effects, and perhaps deleterious effects on brain systems (Upadhyay et al., 2010; Younger et al., 2011 2153107), although further studies are needed to support this. Furthermore, in the acute pain setting, while morphine's analgesic effects are clear, accumulating evidence suggests that the agent may delay wound healing (Rook and McCarson, 2007; Rook et al., 2008, 2009; Martin et al., 2010). The appreciation of brain system involvement in neuropathic pain has led to attempts to try neurostimulation/ neuromodulatory approaches (Turgut and Altun, 2009; Schwenkreis et al., 2010).

5. Conclusions

Approaches to mitigating the potential for patients to have chronic pain following surgery are a medical imperative. As noted, the problem is immense and the opportunity to implement processes in pre-, intra- and post-operative periods may provide substantial benefit. Various preoperative factors may predict poor outcomes preoperatively that include measures of catastrophizing, poor endogenous modulatory systems, genetic measures that may define those who may be predisposed, and gender. Although current intraoperative measures used in an attempt to mitigate the development to diminish SNPP, there still is an urgent need to develop an objective measure of pain in perioperative medicine. . Such measures are important since they define *approaches to knowing if a patient has nociceptive activation and thus the potential for central sensitization and also the ability to appreciate that abnormal function in peripheral nerve may be evident utilizing advanced radiological approaches (Tagliafico et al., 2010)*. If we can 'know' we can 'act' and implement strategies to diminish this chronic burden. Clearly, the preoperative definition of those patients who are at high risk for developing SNPP should be considered as part of anesthesia/surgical evaluation.

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References

American Pain Society (Inc RSW, ed): American Pain Society, The American Academy of Pain Medicine. 1999. Chronic Pain in America: Roadblocks to Relief.

Aasvang EK, Kehlet H. Chronic pain after childhood groin hernia repair. J Pediatr Surg. 2007; 42:1403–1408. [PubMed: 17706504]

Aasvang EK, Kehlet H. Persistent sensory dysfunction in pain-free herniotomy. Acta Anaesthesiol Scand. 2010; 54:291–298. [PubMed: 19839945]

Abbadie C, Bhangoo S, De Koninck Y, Malcangio M, Melik-Parsadaniantz S, White FA. Chemokines and pain mechanisms. Brain Res Rev. 2009; 60:125–134. [PubMed: 19146875]

Alvarez P, Ferrari LF, Levine JD. Muscle pain in models of chemotherapy-induced and alcohol-induced peripheral neuropathy. Ann Neurol. 2011; 70:101–109. [PubMed: 21786301]

Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain. 2011; 152:S49–S64. [PubMed: 21146929]

Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci. 2004; 24:10410–10415. [PubMed: 15548656]

Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998; 280:1831–1836. [PubMed: 9846777]

Baliki MN, Geha PY, Apkarian AV. Parsing pain perception between nociceptive representation and magnitude estimation. J Neurophysiol. 2009; 101:875–887. [PubMed: 19073802]

Bannister K, Dickenson AH. Opioid hyperalgesia. Curr Opin Support Palliat Care. 2010; 4:1–5. [PubMed: 20019618]

Bartocci M, Bergqvist LL, Lagercrantz H, Anand KJ. Pain activates cortical areas in the preterm newborn brain. Pain. 2006; 122:109–117. [PubMed: 16530965]

Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci. 1984; 7:309–338. [PubMed: 6143527]

Becerra L, Harris W, Grant M, George E, Boas D, Borsook D. Diffuse optical tomography activation in the somatosensory cortex: specific activation by painful vs. non-painful thermal stimuli. PLoS One. 2009; 4:e8016. [PubMed: 19956637]

Becerra L, Morris S, Bazes S, Gostic R, Sherman S, Gostic J, Pendse G, Moulton E, Scrivani S, Keith D, Chizh B, Borsook D. Trigeminal neuropathic pain alters responses in CNS circuits to mechanical (brush) and thermal (cold and heat) stimuli. J Neurosci. 2006; 26:10646–10657. [PubMed: 17050704]

Ben-Shlomo Y, Naqvi H, Baker I. Ethnic differences in healthcare-seeking behaviour and management for acute chest pain: secondary analysis of the MINAP dataset 2002–2003. Heart. 2008; 94:354–359. [PubMed: 17591647]

Bischoff P, Drogemeier K, Scholz J, Nahm W, von Knobelsdorff G, Schulte am Esch J. [Electrophysiologic arousal reactions during sufentanil-/isoflurane anesthesia]. Anasthesiol Intensivmed Notfallmed Schmerzther. 1998; 33:88–95. [PubMed: 9558432]

Blusse van Oud-Alblas HJ, van Dijk M, Liu C, Tibboel D, Klein J, Weber F. Intraoperative awareness during paediatric anaesthesia. Br J Anaesth. 2009; 102:104–110. [PubMed: 18987058]

Borgeat A, Aguirre J. Assessment and treatment of postblock neurologic injury. Anesthesiol Clin. 2011; 29:243–256. [PubMed: 21620341]

Borghi B, D'Addabbo M, White PF, Gallerani P, Toccaceli L, Raffaeli W, Tognu A, Fabbri N, Mercuri M. The use of prolonged peripheral neural blockade after lower extremity amputation: the effect on symptoms associated with phantom limb syndrome. Anesth Analg. 2010; 111:1308–1315. [PubMed: 20881281]

Borsook D, Becerra L. How close are we in utilizing functional neuroimaging in routine clinical diagnosis of neuropathic pain? Curr Pain Headache Rep. 2011a; 15:223–229. [PubMed: 21369853]

Borsook D, Becerra L. CNS animal fMRI in pain and analgesia. Neurosci Biobehav Rev. 2011b; 35:1125–1143. [PubMed: 21126534]

Borsook D, Hargreaves R, Becerra L. Can Functional Magnetic Resonance Imaging Improve Success Rates in CNS Drug Discovery? Expert Opin Drug Discov. 2011; 6:597–617. [PubMed: 21765857]

Borsook D, George E, Kussman B, Becerra L. Anesthesia and perioperative stress: consequences on neural networks and postoperative behaviors. Prog Neurobiol. 2010; 92:601–612. [PubMed: 20727935]

Bove GM, Dilley A. The conundrum of sensitization when recording from nociceptors. J Neurosci Methods. 2010; 188:213–218. [PubMed: 20171245]

Buchanan FF, Myles PS, Cicuttini F. Effect of patient sex on general anaesthesia and recovery. Br J Anaesth. 2011; 106:832–839. [PubMed: 21558068]

Cauda F, D'Agata F, Sacco K, Duca S, Cocito D, Paolasso I, Isoardo G, Geminiani G. Altered resting state attentional networks in diabetic neuropathic pain. J Neurol Neurosurg Psychiatry. 2010; 81:806–811. [PubMed: 19955113]

Celestin J, Edwards RR, Jamison RN. Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: a systematic review and literature synthesis. Pain Med. 2009; 10:639–653. [PubMed: 19638142]

Chabal C, Jacobson L, Little J. Effects of intrathecal fentanyl and lidocaine on somatosensory-evoked potentials, the H-reflex, and clinical responses. Anesth Analg. 1988; 67:509–513. [PubMed: 3377205]

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Med. 2004; 5:263–275. [PubMed: 15367304]

Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009; 32:1–32. [PubMed: 19400724]

Costigan M, et al. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain. 2010; 133:2519–2527. [PubMed: 20724292]

Counsell CM, Guin PR, Limbaugh B. Coordinated care for the neuroscience patient: future directions. J Neurosci Nurs. 1994; 26:245–250. [PubMed: 7814918]

Cullen K, Hall MJ, Golosinskiy A. Ambulatory Surgery in the United States, 2006. National Health Statistics Reports. 2009; 11:1–28. [PubMed: 19294964]

Cusick CG. Extensive cortical reorganization following sciatic nerve injury in adult rats versus restricted reorganization after neonatal injury: implications for spatial and temporal limits on somatosensory plasticity. Prog Brain Res. 1996; 108:379–390. [PubMed: 8979815]

Dahl JB, Moiniche S. Pre-emptive analgesia. Br Med Bull. 2004; 71:13–27. [PubMed: 15596866]

Dahl JB, Kehlet H. Preventive analgesia. Curr Opin Anaesthesiol. 2011; 24:331–338. [PubMed: 21478742]

DaSilva AF, Becerra L, Pendse G, Chizh B, Tully S, Borsook D. Colocalized structural and functional changes in the cortex of patients with trigeminal neuropathic pain. PLoS One. 2008; 3:e3396. [PubMed: 18923647]

Dimova V, Lautenbacher S. [Chronic postoperative pain. Epidemiology and psychological risk factors]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2010; 45:488–493. quiz 494. [PubMed: 20665360]

Dobrogowski J, Przeklasa-Muszynska A, Wordliczek J. [Persistent post-operative pain]. Folia Med Cracov. 2008; 49:27–37. [PubMed: 19140488]

Fernandez-Galinski SM, Monells J, Espadaler JM, Pol O, Puig MM. Effects of subarachnoid lidocaine, meperidine and fentanyl on somatosensory and motor evoked responses in awake humans. Acta Anaesthesiol Scand. 1996; 40:39–46. [PubMed: 8904258]

Flierl MA, Stahel PF, Touban BM, Beauchamp KM, Morgan SJ, Smith WR, Ipaktchi KR. Bench-to-bedside review: Burn-induced cerebral inflammation--a neglected entity? Crit Care. 2009; 13:215. [PubMed: 19638180]

Gardell LR, Vanderah TW, Gardell SE, Wang R, Ossipov MH, Lai J, Porreca F. Enhanced evoked excitatory transmitter release in experimental neuropathy requires descending facilitation. J Neurosci. 2003; 23:8370–8379. [PubMed: 12967999]

Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron. 2008; 60:570–581. [PubMed: 19038215]

Gerbershagen HJ, Dagtekin O, Gaertner J, Petzke F, Heidenreich A, Sabatowski R, Ozgur E. Preoperative chronic pain in radical prostatectomy patients: preliminary evidence for enhanced susceptibility to surgically induced pain. Eur J Anaesthesiol. 2010; 27:448–454. [PubMed: 20299992]

Gerbershagen HJ, Ozgur E, Dagtekin O, Straub K, Hahn M, Heidenreich A, Sabatowski R, Petzke F. Preoperative pain as a risk factor for chronic post-surgical pain - six month follow-up after radical prostatectomy. Eur J Pain. 2009; 13:1054–1061. [PubMed: 19138869]

Ghaly RF, Ham JH, Lee JJ. High-dose ketamine hydrochloride maintains somatosensory and magnetic motor evoked potentials in primates. Neurol Res. 2001; 23:881–886. [PubMed: 11760882]

Goff JR, Burkey AR, Goff DJ, Jasmin L. Reorganization of the spinal dorsal horn in models of chronic pain: correlation with behaviour. Neuroscience. 1998; 82:559–574. [PubMed: 9466461]

Granot M, Ferber SG. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. Clin J Pain. 2005; 21:439–445. [PubMed: 16093750]

Grape S, Tramer MR. Do we need preemptive analgesia for the treatment of postoperative pain? Best Pract Res Clin Anaesthesiol. 2007; 21:51–63. [PubMed: 17489219]

Gray P. Acute neuropathic pain: diagnosis and treatment. Curr Opin Anaesthesiol. 2008; 21:590–595. [PubMed: 18784484]

Guastella V, Mick G, Soriano C, Vallet L, Escande G, Dubray C, Eschalier A. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. Pain. 2011; 152:74–81. [PubMed: 21075523]

Gwilym SE, Filippini N, Douaud G, Carr AJ, Tracey I. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. Arthritis Rheum. 2010; 62:2930–2940. [PubMed: 20518076]

Hall MJDC, Williams SN, Golosinskiy A, Schwartzman A. National Hospital Discharge Survey: 2007 Summary. National Health Statistics Reports. 2010; 29:1–21. [PubMed: 21086860]

Haller G, Laroche T, Clergue F. Morbidity in anaesthesia: today and tomorrow. Best Pract Res Clin Anaesthesiol. 2011; 25:123–132. [PubMed: 21550538]

Hanley MA, Jensen MP, Smith DG, Ehde DM, Edwards WT, Robinson LR. Preamputation pain and acute pain predict chronic pain after lower extremity amputation. J Pain. 2007; 8:102–109. [PubMed: 16949876]

Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum. 2008; 58:903–907. [PubMed: 18311814]

Hinrichs-Rocker A, Schulz K, Jarvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - a systematic review. Eur J Pain. 2009; 13:719–730. [PubMed: 18952472]

Hogan QH. Pathophysiology of peripheral nerve injury during regional anesthesia. Reg Anesth Pain Med. 2008; 33:435–441. [PubMed: 18774512]

Hummel M, Lu P, Cummons TA, Whiteside GT. The persistence of a long-term negative affective state following the induction of either acute or chronic pain. Pain. 2008; 140:436–445. [PubMed: 18945547]

Ilfeld BM. Continuous Peripheral Nerve Blocks: A Review of the Published Evidence. Anesth Analg. 2011

Karanikolas M, Aretha D, Tsolakis I, Monantera G, Kiekkas P, Papadoulas S, Swarm RA, Filos KS. Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency: a prospective, randomized, clinical trial. Anesthesiology. 2011; 114:1144–1154. [PubMed: 21368651]

Katz J, McCartney CJ. Current status of preemptive analgesia. Curr Opin Anaesthesiol. 2002; 15:435–441. [PubMed: 17019235]

Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009; 9:723–744. [PubMed: 19402781]

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006; 367:1618–1625. [PubMed: 16698416]

Khan RS, Ahmed K, Blakeway E, Skapinakis P, Nihoyannopoulos L, Macleod K, Sevdalis N, Ashrafian H, Platt M, Darzi A, Athanasiou T. Catastrophizing: a predictive factor for postoperative pain. Am J Surg. 2011; 201:122–131. [PubMed: 20832052]

Kochs E, Treede RD, Schulte am Esch J, Bromm B. Modulation of pain-related somatosensory evoked potentials by general anesthesia. Anesth Analg. 1990; 71:225–230. [PubMed: 2393105]

Kolesnikov Y, El-Maarouf A, Rutishauser U, Pasternak G. Reorganization of dorsal root ganglion neurons following chronic sciatic nerve constriction injury: correlation with morphine and lidocaine analgesia. Eur J Pharmacol. 2007; 568:124–133. [PubMed: 17543299]

Kristensen AD, Pedersen TA, Hjortdal VE, Jensen TS, Nikolajsen L. Chronic pain in adults after thoracotomy in childhood or youth. Br J Anaesth. 2010; 104:75–79. [PubMed: 19915188]

Kumar S, Wilson RG, Nixon SJ, Macintyre IM. Chronic pain after laparoscopic and open mesh repair of groin hernia. Br J Surg. 2002; 89:1476–1479. [PubMed: 12390395]

Lautenbacher S, Huber C, Baum C, Rossaint R, Hochrein S, Heesen M. Attentional avoidance of negative experiences as predictor of postoperative pain ratings and consumption of analgesics: comparison with other psychological predictors. Pain Med. 2011; 12:645–653. [PubMed: 21392251]

Lenz M, Hoffken O, Stude P, Lissek S, Schwenkreis P, Reinersmann A, Frettloh J, Richter H, Tegenthoff M, Maier C. Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I. Neurology. 2011; 77:1096–1101. [PubMed: 21880999]

Leo RJ, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review. J Pain. 2007; 8:453–459. [PubMed: 17434804]

Leslie K, Davidson AJ. Awareness during anesthesia: a problem without solutions? Minerva Anestesiol. 2010; 76:624–628. [PubMed: 20661203]

Leslie K, Chan MT, Myles PS, Forbes A, McCulloch TJ. Posttraumatic stress disorder in aware patients from the B-aware trial. Anesth Analg. 2010; 110:823–828. [PubMed: 19861364]

Li JY, Xie W, Strong JA, Guo QL, Zhang JM. Mechanical hypersensitivity, sympathetic sprouting, and glial activation are attenuated by local injection of corticosteroid near the lumbar ganglion in a rat model of neuropathic pain. Reg Anesth Pain Med. 2011; 36:56–62. [PubMed: 21455091]

Loix S, De Kock M, Henin P. The anti-inflammatory effects of ketamine: state of the art. Acta Anaesthesiol Belg. 2011; 62:47–58. [PubMed: 21612145]

Loos MJ, Roumen RM, Scheltinga MR. Chronic sequelae of common elective groin hernia repair. Hernia. 2007; 11:169–173. [PubMed: 17279317]

Lund C, Selmar P, Hansen OB, Kehlet H. Effect of intrathecal bupivacaine on somatosensory evoked potentials following dermatomal stimulation. Anesth Analg. 1987; 66:809–813. [PubMed: 3039873]

Lynch ME, Campbell FA, Clark AJ, Dunbar MJ, Goldstein D, Peng P, Stinson J, Tupper H. Waiting for treatment for chronic pain - a survey of existing benchmarks: toward establishing evidence-based benchmarks for medically acceptable waiting times. Pain Res Manag. 2007; 12:245–248. [PubMed: 18080042]

Lynch ME, Campbell F, Clark AJ, Dunbar MJ, Goldstein D, Peng P, Stinson J, Tupper H. A systematic review of the effect of waiting for treatment for chronic pain. Pain. 2008; 136:97–116. [PubMed: 17707589]

Maihofner C, Nickel FT, Seifert F. [Neuropathic pain and neuroplasticity in functional imaging studies]. Schmerz. 2010; 24:137–145. [PubMed: 20376602]

Malviya S, Galinkin JL, Bannister CF, Burke C, Zuk J, Popenhagen M, Brown S, Voepel-Lewis T. The incidence of intraoperative awareness in children: childhood awareness and recall evaluation. Anesth Analg. 2009; 109:1421–1427. [PubMed: 19713260]

Manchikanti L, Singh V. Managing phantom pain. Pain Physician. 2004; 7:365–375. [PubMed: 16858476]

Martin CM. When medications make pain worse: opioid-induced hyperalgesia. Consult Pharm. 2011; 26:530–542. [PubMed: 21840817]

Martin JL, Koodie L, Krishnan AG, Charboneau R, Barke RA, Roy S. Chronic morphine administration delays wound healing by inhibiting immune cell recruitment to the wound site. Am J Pathol. 2010; 176:786–799. [PubMed: 20042674]

Massaron S, Bona S, Fumagalli U, Battafarano F, Elmore U, Rosati R. Analysis of post-surgical pain after inguinal hernia repair: a prospective study of 1,440 operations. Hernia. 2007; 11:517–525. [PubMed: 17646895]

May A. Structural brain imaging: a window into chronic pain. Neuroscientist. 2011; 17:209–220. [PubMed: 21489967]

McCracken LM, Matthews AK, Tang TS, Cuba SL. A comparison of blacks and whites seeking treatment for chronic pain. Clin J Pain. 2001; 17:249–255. [PubMed: 11587117]

McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. J Trauma. 2008; 64:S195–S198. Discussion S197–198. [PubMed: 18376165]

McKenzie LH, Simpson J, Stewart M. A systematic review of pre-operative predictors of post-operative depression and anxiety in individuals who have undergone coronary artery bypass graft surgery. Psychol Health Med. 2010; 15:74–93. [PubMed: 20391226]

Mikkelsen T, Werner MU, Lassen B, Kehlet H. Pain and sensory dysfunction 6 to 12 months after inguinal herniotomy. Anesth Analg. 2004; 99:146–151. [PubMed: 15281521]

Millan MJ. The induction of pain: an integrative review. Prog Neurobiol. 1999; 57:1–164. [PubMed: 9987804]

Moalem G, Tracey DJ. Immune and inflammatory mechanisms in neuropathic pain. Brain Res Rev. 2006; 51:240–264. [PubMed: 16388853]

Myers RR, Campana WM, Shubayev VI. The role of neuroinflammation in neuropathic pain: mechanisms and therapeutic targets. Drug Discov Today. 2006; 11:8–20. [PubMed: 16478686]

Neumann S, Doubell TP, Leslie T, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature. 1996; 384:360–364. [PubMed: 8934522]

Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet. 1997a; 350:1353–1357. [PubMed: 9365449]

Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. Pain. 1997b; 72:393–405. [PubMed: 9313280]

O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics. 2009; 27:95–112. [PubMed: 19254044]

Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg. 2005; 100:757–773. table of contents. [PubMed: 15728066]

Ozgur E, Straub K, Wille S, Engelmann U, Dagtekin O, Gerbershagen HJ. [Impact of preoperative pain on postoperative pain chronification : Six-month follow-up after urologic surgery.]. Urologe A. 2011

Pabreja K, Dua K, Sharma S, Padi SS, Kulkarni SK. Minocycline attenuates the development of diabetic neuropathic pain: possible anti-inflammatory and anti-oxidant mechanisms. Eur J Pharmacol. 2011; 661:15–21. [PubMed: 21536024]

Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G, Palgimesi A. The role of catastrophizing in the prediction of postoperative pain. Pain Med. 2009; 10:1452–1459. [PubMed: 19863742]

Pavlin DJ, Sullivan MJ, Freund PR, Roesen K. Catastrophizing: a risk factor for postsurgical pain. Clin J Pain. 2005; 21:83–90. [PubMed: 15599135]

Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology. 2000; 93:1123–1133. [PubMed: 11020770]

Peyron R, Faillenot I. [Functional brain mapping of pain perception]. Med Sci (Paris). 2011; 27:82–87. [PubMed: 21299967]

Pies R. How "objective" are psychiatric diagnoses?: (guess again). Psychiatry (Edgmont). 2007; 4:18–22. [PubMed: 20428307]

Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. Curr Opin Anaesthesiol. 2006; 19:551–555. [PubMed: 16960490]

Poobalan AS, Bruce J, Smith WC, King PM, Krukowski ZH, Chambers WA. A review of chronic pain after inguinal herniorrhaphy. Clin J Pain. 2003; 19:48–54. [PubMed: 12514456]

Powell AE, Davies HT, Bannister J, Macrae WA. Challenge of improving postoperative pain management: case studies of three acute pain services in the UK National Health Service. Br J Anaesth. 2009; 102:824–831. [PubMed: 19376790]

Price S. Pain: Resolvins show promise for treating inflammatory pain. Nat Rev Rheumatol. 2010; 6:379. [PubMed: 20614500]

Rahim-Williams FB, Rileya JL 3rd, Herrera D, Campbell CM, Hastie BA, Fillingim RB. Ethnic identity predicts experimental pain sensitivity in African Americans and Hispanics. Pain. 2007; 129:177–184. [PubMed: 17296267]

Raja SN, Jensen TS. Predicting postoperative pain based on preoperative pain perception: are we doing better than the weatherman? Anesthesiology. 2010; 112:1311–1312. [PubMed: 20502114]

Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. J Neurosci. 2009; 29:13746–13750. [PubMed: 19889986]

Rook JM, McCarson KE. Delay of cutaneous wound closure by morphine via local blockade of peripheral tachykinin release. Biochem Pharmacol. 2007; 74:752–757. [PubMed: 17632084]

Rook JM, Hasan W, McCarson KE. Temporal effects of topical morphine application on cutaneous wound healing. Anesthesiology. 2008; 109:130–136. [PubMed: 18580183]

Rook JM, Hasan W, McCarson KE. Morphine-induced early delays in wound closure: involvement of sensory neuropeptides and modification of neurokinin receptor expression. Biochem Pharmacol. 2009; 77:1747–1755. [PubMed: 19428329]

Rosenberger PH, Jokl P, Ickovics J. Psychosocial factors and surgical outcomes: an evidence-based literature review. J Am Acad Orthop Surg. 2006; 14:397–405. [PubMed: 16822887]

Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA. 1998; 280:1837–1842. [PubMed: 9846778]

Rubino LJ, Konstantakos EK, Stills HF Jr, Dudley ES, Grunden BK, Malaviya P. Healing of iatrogenic skeletal muscle wounds is affected by incision device. Surg Innov. 2010; 17:85–91. [PubMed: 20504782]

Rundshagen I, Kochs E, Bischoff P, Schulte am Esch J. [Intraoperative pain stimuli change somatosensory evoked potentials, but not auditory evoked potentials during isoflurane/nitrous oxide anesthesia]. Anasthesiol Intensivmed Notfallmed Schmerzther. 1997; 32:604–609. [PubMed: 9401096]

Saab CY, Waxman SG, Hains BC. Alarm or curse? The pain of neuroinflammation. Brain Res Rev. 2008; 58:226–235. [PubMed: 18486228]

Schaible HG. Peripheral and central mechanisms of pain generation. Handb Exp Pharmacol. 2007:3–28. [PubMed: 17087118]

Schley M, Topfner S, Wiech K, Schaller HE, Konrad CJ, Schmelz M, Birbaumer N. Continuous brachial plexus blockade in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. Eur J Pain. 2007; 11:299–308. [PubMed: 16716615]

Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. Nat Neurosci. 2007; 10:1361–1368. [PubMed: 17965656]

Schott GD. Delayed onset and resolution of pain: some observations and implications. Brain. 2001; 124:1067–1076. [PubMed: 11353723]

Schwenkreis P, Scherens A, Ronnau AK, Hoffken O, Tegenthoff M, Maier C. Cortical disinhibition occurs in chronic neuropathic, but not in chronic nociceptive pain. BMC Neurosci. 2010; 11:73. [PubMed: 20540759]

Seifert F, Maihofner C. Functional and structural imaging of pain-induced neuroplasticity. Curr Opin Anaesthesiol. 2011

Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci. 2011; 31:7540–7550. [PubMed: 21593339]

Shipton EA, Tait B. Flagging the pain: preventing the burden of chronic pain by identifying and treating risk factors in acute pain. Eur J Anaesthesiol. 2005; 22:405–412. [PubMed: 15991501]

Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009; 145:304–311. [PubMed: 19604642]

Sivilotti LG, Thompson SW, Woolf CJ. Rate of rise of the cumulative depolarization evoked by repetitive stimulation of small-caliber afferents is a predictor of action potential windup in rat spinal neurons in vitro. J Neurophysiol. 1993; 69:1621–1631. [PubMed: 8389833]

Slater R, Cantarella A, Gallella S, Worley A, Boyd S, Meek J, Fitzgerald M. Cortical pain responses in human infants. J Neurosci. 2006; 26:3662–3666. [PubMed: 16597720]

Smith WC, Bourne D, Squair J, Phillips DO, Chambers WA. A retrospective cohort study of post mastectomy pain syndrome. Pain. 1999; 83:91–95. [PubMed: 10506676]

Sorenson EJ. Neurological injuries associated with regional anesthesia. Reg Anesth Pain Med. 2008; 33:442–448. [PubMed: 18774513]

Sotgiu ML, Biella G, Riva L. A study of early ongoing activity in dorsal horn units following sciatic nerve constriction. Neuroreport. 1994; 5:2609–2612. [PubMed: 7696614]

Staff NP, Engelstad J, Klein CJ, Amrami KK, Spinner RJ, Dyck PJ, Warner MA, Warner ME. Post-surgical inflammatory neuropathy. Brain. 2010; 133:2866–2880. [PubMed: 20846945]

Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. Pain. 2007; 129:130–142. [PubMed: 17156923]

Steegers MA, Snik DM, Verhagen AF, van der Drift MA, Wilder-Smith OH. Only half of the chronic pain after thoracic surgery shows a neuropathic component. J Pain. 2008; 9:955–961. [PubMed: 18632308]

Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics, and impact of postmastectomy pain syndrome: an investigation of women's experiences. Pain. 1995; 61:61–68. [PubMed: 7644250]

Taddio A, Goldbach M, Ipp M, Stevens B, Koren G. Effect of neonatal circumcision on pain responses during vaccination in boys. Lancet. 1995; 345:291–292. [PubMed: 7837863]

Tagliafico A, Altafini L, Garello I, Marchetti A, Gennaro S, Martinoli C. Traumatic neuropathies: spectrum of imaging findings and postoperative assessment. Semin Musculoskelet Radiol. 2010; 14:512–522. [PubMed: 21072729]

Tegeder I, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med. 2006; 12:1269–1277. [PubMed: 17057711]

Thacker MA, Clark AK, Marchand F, McMahon SB. Pathophysiology of peripheral neuropathic pain: immune cells and molecules. Anesth Analg. 2007; 105:838–847. [PubMed: 17717248]

Tinnin L. Conscious forgetting and subconscious remembering of pain. J Clin Ethics. 1994; 5:151–152. [PubMed: 7919488]

Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007; 55:377–391. [PubMed: 17678852]

Turgut N, Altun BU. Cortical disinhibition in diabetic patients with neuropathic pain. Acta Neurol Scand. 2009; 120:383–388. [PubMed: 19922582]

Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, Wallin D, Pendse G, McDonald L, Griffin M, Anderson J, Nutile L, Renshaw P, Weiss R, Becerra L, Borsook D. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain. 2010; 133:2098–2114. [PubMed: 20558415]

Van der Vleuten CP, Norman GR, De Graaff E. Pitfalls in the pursuit of objectivity: issues of reliability. Med Educ. 1991; 25:110–118. [PubMed: 2023552]

VanDenKerkhof EG, Hopman WM, Towheed T, Wilson R, Murdoch J, Rimmer M, Stutzman SS, Tod D, Dagnone V, Goldstein DH. Pain, health-related quality of life and health care utilization after inpatient surgery: a pilot study. Pain Res Manag. 2006; 11:41–47. [PubMed: 16511613]

Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. The postmastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. Br J Cancer. 2008; 99:604–610. [PubMed: 18682712]

Voscopoulos C, Lema M. When does acute pain become chronic? Br J Anaesth. 2010; 105(Suppl 1):i69–i85. [PubMed: 21148657]

Walco GA, Dworkin RH, Krane EJ, LeBel AA, Treede RD. Neuropathic pain in children: Special considerations. Mayo Clin Proc. 2010; 85:S33–S41. [PubMed: 20194147]

Wall PD. Neuropathic pain and injured nerve: central mechanisms. Br Med Bull. 1991; 47:631–643. [PubMed: 1794076]

Welters ID, Feurer MK, Preiss V, Muller M, Scholz S, Kwapisz M, Mogk M, Neuhauser C. Continuous S-(+)-ketamine administration during elective coronary artery bypass graft surgery

attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass. Br J Anaesth. 2011; 106:172–179. [PubMed: 21138901]

Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006; 67:1411–1420. [PubMed: 17060567]

Wiesenfeld-Hallin Z. Sex differences in pain perception. Gend Med. 2005; 2:137–145. [PubMed: 16290886]

Wilson JA, Nimmo AF, Fleetwood-Walker SM, Colvin LA. A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. Pain. 2008; 135:108–118. [PubMed: 17583431]

Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011; 152:S2–S15. [PubMed: 20961685]

Woolf CJ, Chong MS. Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993; 77:362–379. [PubMed: 8346839]

Wu G, Ringkamp M, Hartke TV, Murinson BB, Campbell JN, Griffin JW, Meyer RA. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. J Neurosci. 2001; 21:RC140. [PubMed: 11306646]

Wu G, Ringkamp M, Murinson BB, Pogatzki EM, Hartke TV, Weerahandi HM, Campbell JN, Griffin JW, Meyer RA. Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. J Neurosci. 2002; 22:7746–7753. [PubMed: 12196598]

Xiao WH, Bennett GJ. Persistent low-frequency spontaneous discharge in A-fiber and C-fiber primary afferent neurons during an inflammatory pain condition. Anesthesiology. 2007; 107:813–821. [PubMed: 18073557]

Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol. 2001; 429:23–37. [PubMed: 11698024]

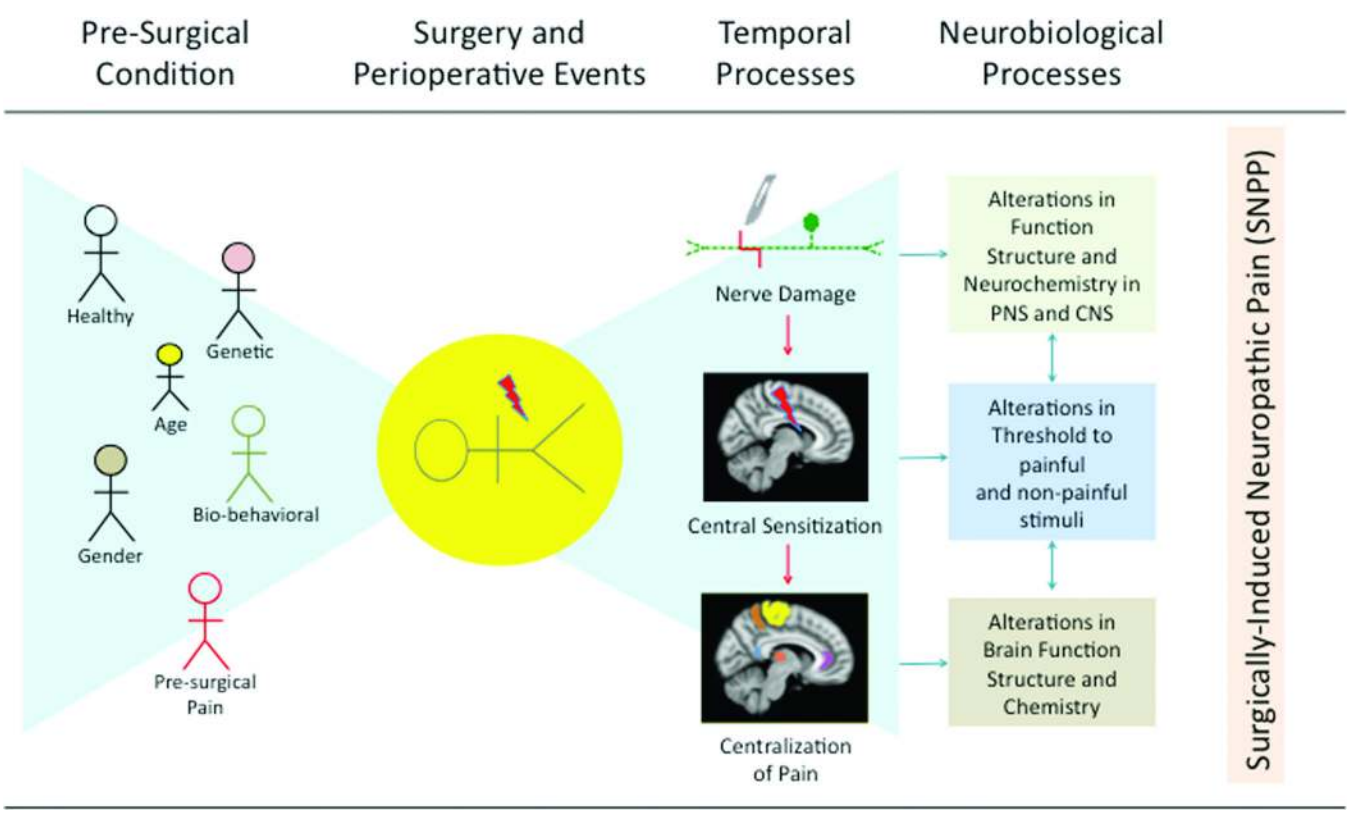

Figure 1. Overall Concepts

1. Pre-surgical condition. Patients may have premorbid conditions including ongoing acute or chronic pain, psychobiological or genetic conditions that may predispose to chronic pain following nerve damage.
2. Surgery and Perioperative Events. Surgery may set of a cascade of events including pain. Pain is not always prevented during surgery and complete pain control is difficult to obtain throughout the perioperative process.
3. Temporal Processes. A cascade of events unfold – after nerve damage aside from afferent bursts of activity that travel to the CNS the nerve begins to unfold that includes central sensitization, a process that may be concurrent with nerve damage and in the perioperative period or as the neuropathic pain state, and centralization of pain where alterations in the CNS take place (see Text). . Most of these brain changes are difficult to reverse by medications. One surgical example relates to removing pain sources in a chronic nociceptive pain syndrome, hip osteoarthritis, where brain changes in cortical volume can be reversed by hip arthroplasty (see (Rodriguez-Raecke et al., 2009; Gwilym et al., 2010)
4. Neurobiological Processes. Following surgical trauma a number of events occur secondary to nerve damage as noted. In the peripheral nerve and spinal cord a number of processes occur including ectopic generation pain potentials, facilitation and disinhibition of pain transmission, loss of synaptic connectivity and formation of new synaptic circuits (Costigan et al., 2009). More centrally (i.e., CNS) facilitation or disinhibition of modulatory circuits is observed in the brainstem (Gardell et al., 2003) or in cortical regions (Schwenkreis et al., 2010; Lenz et al., 2011) (see Text).

Figure 2. Nociception and Pain in the Perioperative Period

Damage to the nerve and nociceptive afferent barrage in the pre-, intra- and postoperative period may contribute to central sensitization and result in changes in the peripheral and central nervous system. Ideally, minimal or no pain should be experienced throughout the perioperative period. However, pain may either be a significant problem during anesthesia (not measured) and/or postoperatively. Complicating any of these patterns is any premorbid pain process. Any barrage of pain may contribute to central sensitization and potentially the chronification from acute pain to chronic pain (See Text).

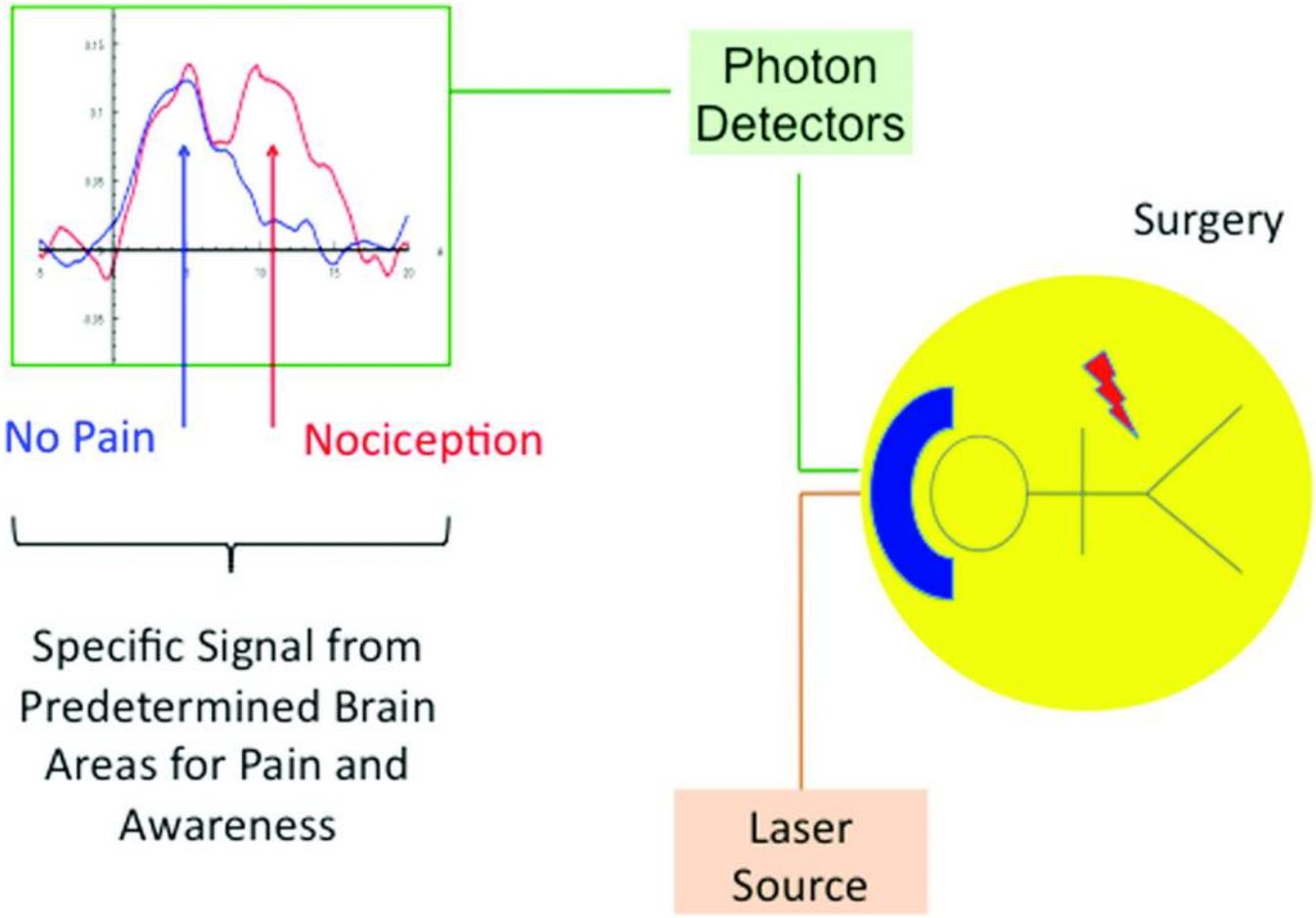

Figure 3. Intermittent Nociceptor Activation (fiber burst activity) across the perioperative state

Shown in this figure are types of pain that may be produced during the perioperative period. Type 1, probably the most severe, results from actual nerve damage and inflammation resulting from surgical trauma. Type 2, is a result of analgesic wear-off during surgery. Type 3 is similar to Type 2, but is present in the post-operative period. The latter may be a result of ongoing nociceptive pain during recovery or the result of neuropathic pain. Different activation patterns may be observed across the peri-operative perioid (see B below).

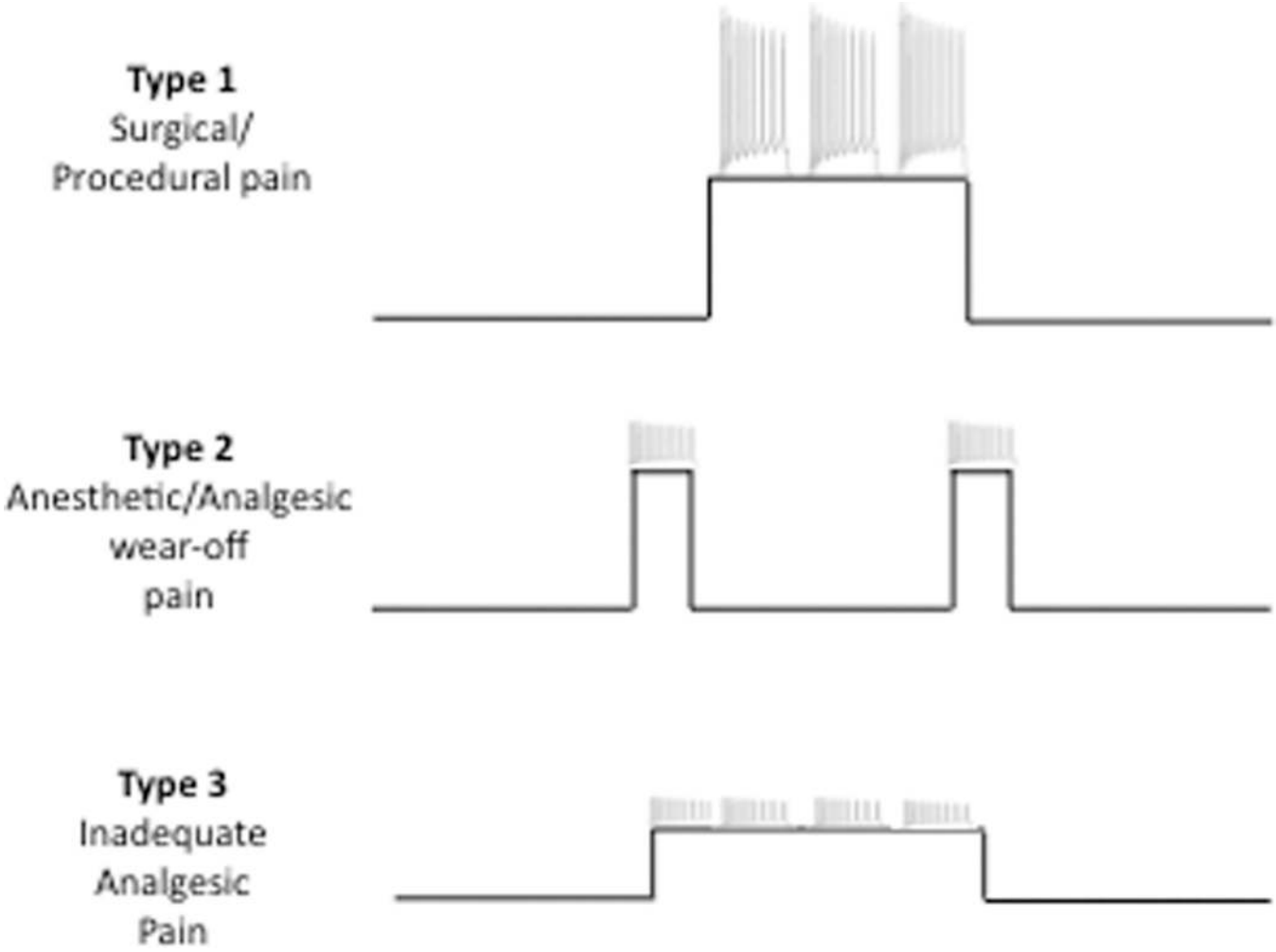

Figure 4. Development of Objective Markers for Nociception (and Pain) and Awareness in the Operating Room

Measures of brain function that can accurately define intraoperative nociceptive activation in brain regions would allow for improved measures of analgesia during surgery. Such changes may have implications for diminishing central sensitization in the postoperative period and potentially limit changes that may contribute to long-term neuropathic pain.