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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 persistent 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;

Ozgun 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 SNPP, 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 antiinflammatory effects (Loix et al., 2011), may help diminish surgical and postsurgical inflammation 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 McCarron, 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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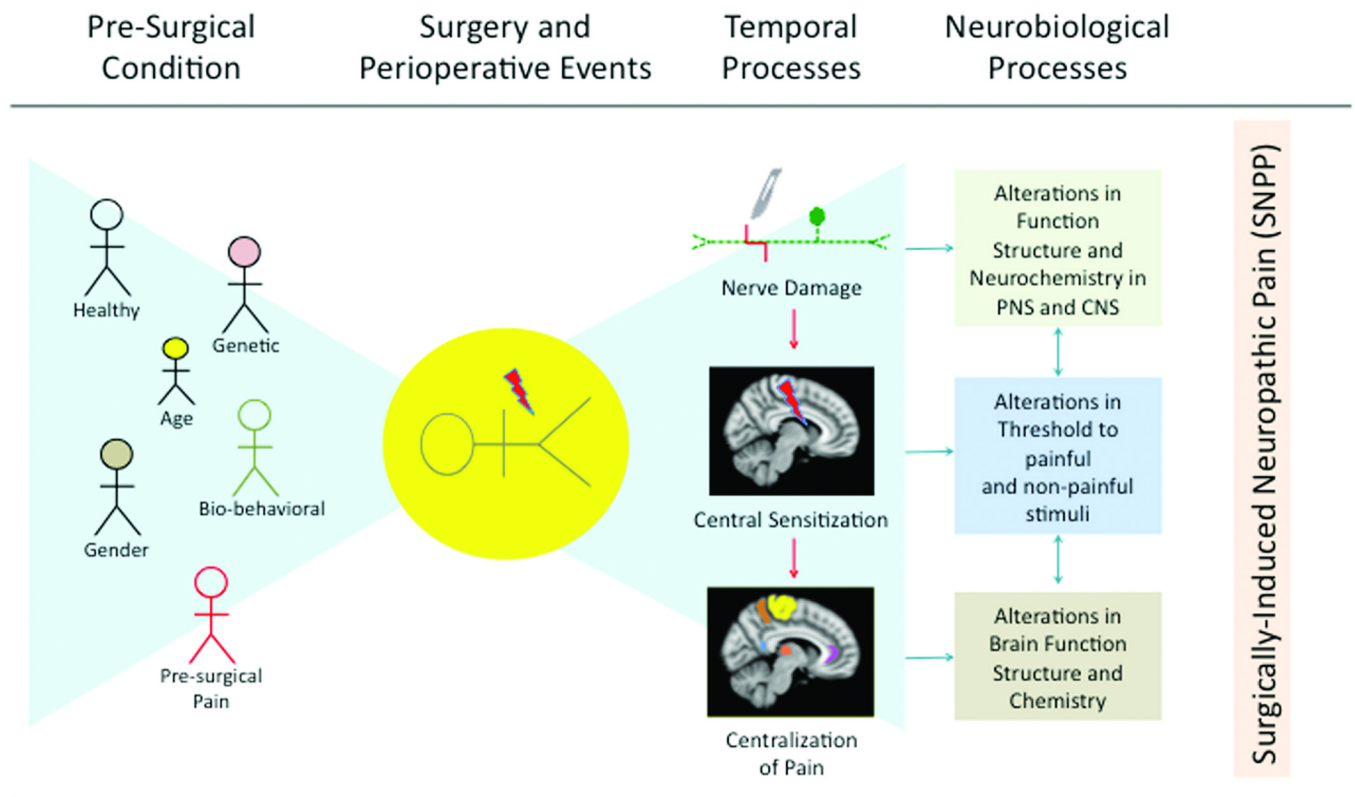


Figure 1. Overall Concepts

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).

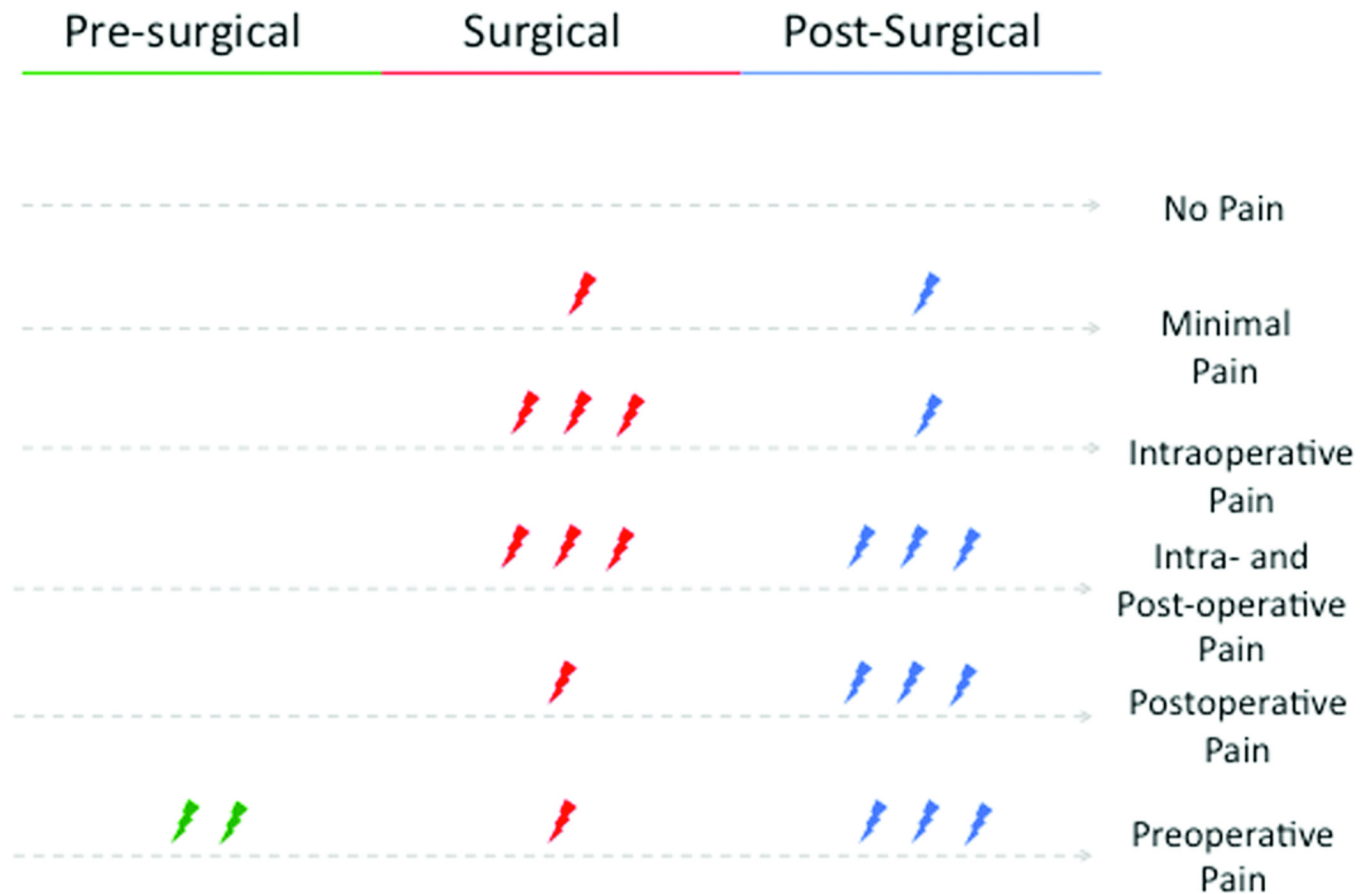


Figure 2. Nociception and Pain in the Perioperative Period

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).

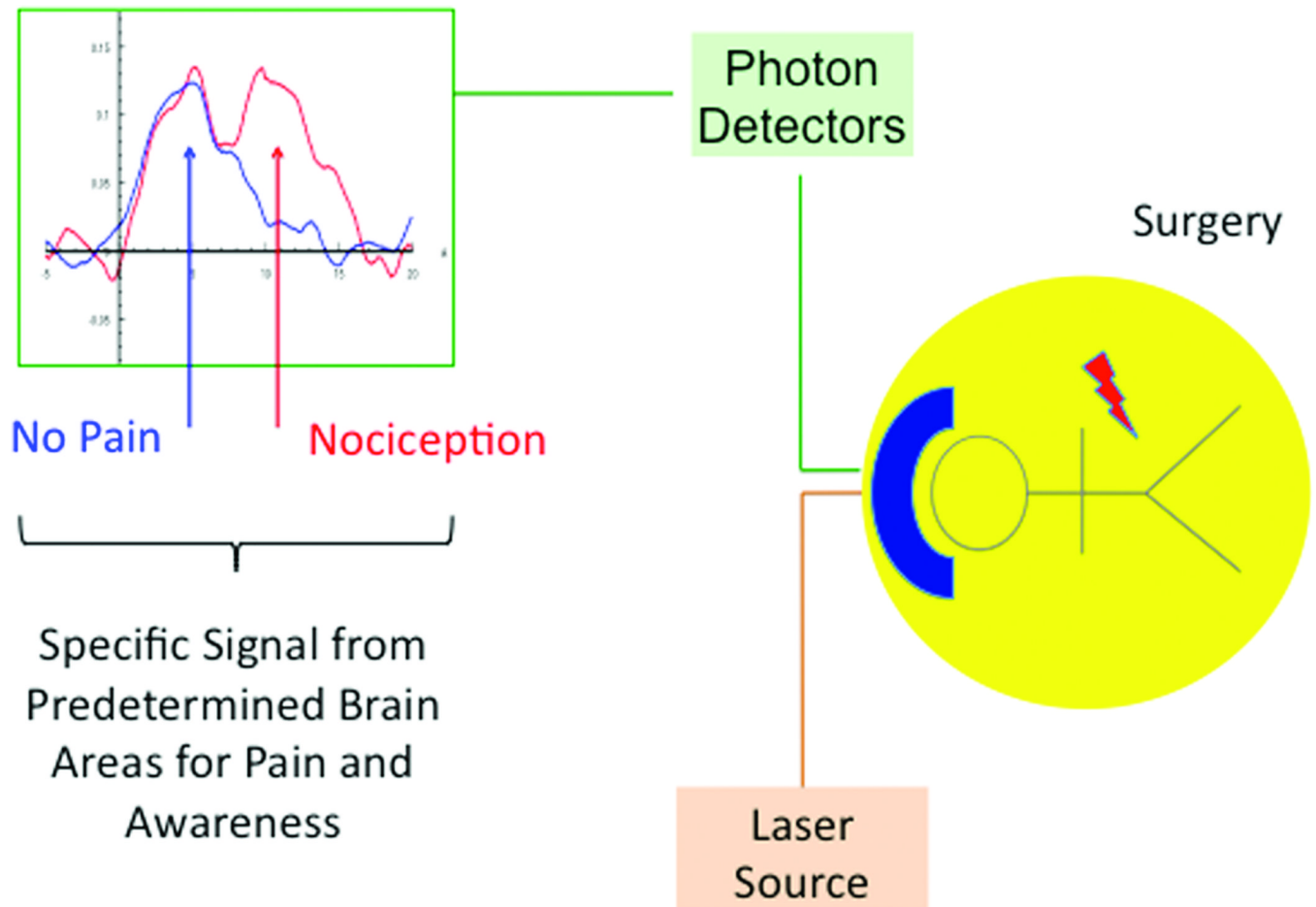


Figure 3. Intermittent Nociceptor Activation (fiber burst activity) across the perioperative state
 Shown in this figure are types of pain that may be produced during the perioperative period. Type 1, probably the most severe, results from actual nerve damage and inflammation resulting from surgical 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 period (see B below).

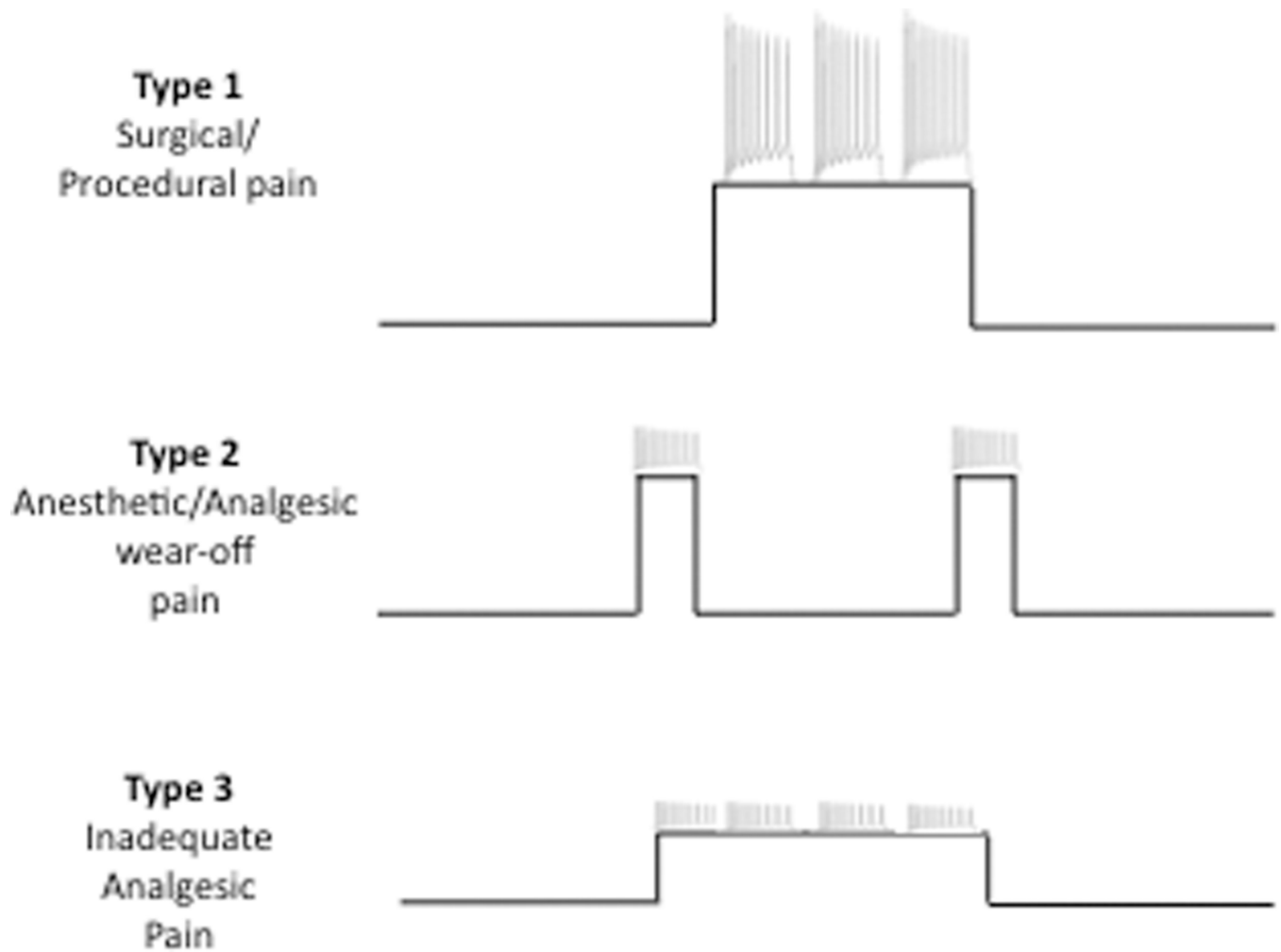


Figure 4. Development of Objective Markers for Nociception (and Pain) and Awareness in the Operating Room

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.