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EXPERT REVIEWS

Mimicking the brain: evaluation of St Jude Medical's Prodigy Chronic Pain System with Burst Technology

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The Prodigy is a new type of internal pulse generator that controls the delivery of electrical stimuli to nervous tissue. It is capable of delivering burst stimulation, which is a novel waveform that consists of closely spaced high-frequency electrical impulses delivered in packets riding on a plateau, and followed by a quiescent period. Its inception was based on mimicking burst firing in the nervous system and usually delivered by unmyelinated fibers that uniformly have a motivational affective homeostatic function. It thereby targets a multimodal salience network, even though the stimuli are delivered at the level of the spinal cord. As such, it is specifically capable of influencing the affective/attentional components of pain. Burst stimulation was initially safely applied off-label to the auditory cortex for tinnitus, and later also to the spinal cord, the somatosensory cortex for neuropathic pain, subcutaneously for failed back surgery syndrome, and cingulate cortex for addiction and tinnitus.

Overview of the market

The current neuromodulation devices market is limited in its versatility and in the current world of electronics and information technology can be considered medieval, using technology originally developed for pacemaker technology [1]. The pacemaker technology was adjusted to stimulating nervous tissue, but never specifically designed for it. There are basically two kinds of spinal cord stimulators, constant current (St Jude Medical and Boston Scientific) and constant voltage (Medtronic) internal pulse generators, both delivering tonic pulses, charge balanced after each positive pulse. The only modifications that can be programmed into the stimulation design are the pulse width, the frequency and the amplitude. In most devices, the output in all channels is the same, even though one internal pulse generator (Boston Scientific) is capable of delivering different stimulation settings for each individual channel, improving flexibility of the delivered stimulation. Whereas traditionally relatively low frequencies are used, averaging around 40–50 Hz for spinal cord stimulation (SCS), recently high-frequency stimulation with paresthesia-free pain suppression has been brought to the market, using 10,000 Hz stimulation with small pulse widths (30 µs) [2]. This, however, has not been tested in a placebo-controlled way.

Rationale of developing burst enabled internal pulse generator?

Conceptually, the nervous system uses at least two firing patterns to transmit information, tonic and burst firing. Therefore, it makes sense to develop a neurostimulator that is capable of mimicking both these firing patterns, that is, to develop a neurostimulator that is especially made for modulating activity and connectivity in the nervous system, and not a derivative of pacemakers. The current implanted pulse generators are only able to deliver tonic charge balanced stimuli,
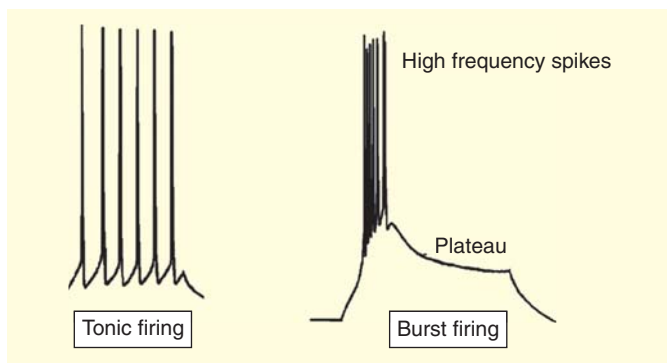
Figure 1. Tonic firing and burst firing.

mimicking tonic firing in the brain (FIGURE 1A). However, some neurons can also fire in bursts, that is, by trains of action potentials that occur during a plateau or active phase, followed by a period of relative quiescence called the silent phase (FIGURE 1B) [3]. The plateau is generated by calcium influx via T-channels, on which sodium spikes are riding [4–6].

The late Antoni Gaudi is probably the most famous Catalan architect, and in his yet unfinished masterpiece the Sagrada Familia cathedral hangs a sign that reads: "*the architect of the future shall construct by mimicking nature because it is a more rational, longer lasting, and more economical method (of building)*". Based on this philosophy, it was proposed that mimicking burst firing electronically would also be a rational way of performing neuromodulation. Thus, a novel stimulation paradigm was developed, called burst stimulation (FIGURE 2) [7]. The concept was to mimic burst firing, which has multiple very interesting features that might make it ideal as a stimulation design, on the condition that an internal pulse generator can be made that is capable of delivering these bursts, which is why the Prodigy (St Jude Medical, Plano, TX, USA) was developed (FIGURE 3).

Table 1. External specifications of the Prodigy with burst technology.

Characteristics	
Height	4.8 cm (1.89 inch)
Length	5.3 cm (3.09 inch)
Thickness	0.95 to 1.1 cm (0.37 to 0.43 inch)
Weight	29.0 g (1.0 oz)
Volume	17.7 cm^3 (1.08 in^3)
Power source	Rechargeable lithium ion cell
Storage temperature	-10–55°C (14–131°F)
Storage humidity	10 to 90% (noncondensing)
Storage pressure	70–150 kPa (10.2–21.8 psi)
Connector strength	Exceeds EN45502-1 requirements

Specifications of the Prodigy

The Prodigy externally is similar to any other internal pulse generator. It has a titanium casing, with silicone header for the insertion of two leads, with a maximum of 16 electrode poles (TABLE 1). Internally, the Prodigy is a further development of the neurodynamics chip that is running ST Jude Medical EON® devices (TABLE 2). It can deliver both tonic and burst mode, important for programming. Usually, the patients are initially programmed in tonic mode, so as to cover the painful area with paresthesia, as is routinely performed in SCS. Once the painful area is covered, the stimulation design is switched to burst mode and amplitude is selected that elicits paresthesia; the amplitude is decreased to 80% of the paresthesia threshold level and further adjusted to the patient's individual specifications.

For SCS, the patient's internal pulse generator is routinely programmed at 40 Hz burst mode with 500 Hz spike mode, using spikes at 1000 μs pulse width [7–9], whereas for somatosensory cortex 4–8 Hz burst mode with 500 Hz spike mode is used [10]. Ultimately, the goal is to mimic natural and physiological burst firing, adjusting programming to the target tissue.

The development of the burst enabling technology

Burst stimulation was developed for treating noise-like tinnitus via implanted electrodes overlying the auditory cortex. It was quickly noted that these implants could only suppress pure tone tinnitus, but had no tinnitus-suppressing effect on noise-like tinnitus [11,12]. The first paper published using burst stimulation was actually on a side effect induced by stimulating the posterior part of the superior temporal gyrus in a tinnitus patient. He developed an out-of-body experience, in a placebo-controlled way, whenever the two most posterior contacts, overlying the right temporoparietal junction, were activated in burst mode, and only in burst mode [13]. Subsequently, the data were published that burst stimulation was superior to tonic stimulation in suppressing noise-like tinnitus [14], later confirmed in a larger study [15]. The underlying idea was that the human auditory system consists of two main parallel pathways supplying auditory information to the cerebral cortex: the parvalbumin staining lemniscal and calbindin staining extralemniscal system [16]. In animals, the parvalbumin pathway is more direct and terminates in the ventral part of the medial geniculate body. Its neurons are sharply tuned, tonotopically organized and consistent in their responses [17,18] and fire predominantly in tonic mode [19,20]. The calbindin pathway is more diffuse in its origins and terminates in the dorsal and medial nuclei [17]. Neurons in the dorsal and medial nuclei are not frequency specific or tonotopic and are labile in their responses [17,21]. They fire more in burst mode [19,20] and project more diffusely to belt areas of the auditory cortex in which parvalbumin immunoreactivity is reduced and in which neuronal responses are less specific than in the core. It was hypothesized that white noise tinnitus may be caused by increased burst firing in the non-tonotopic (extralemniscal) system, whereas pure tone tinnitus may be the result of increased tonic firing in the tonotopic

(lemniscal) system [22,23]. Narrow-band tinnitus could be the result of a co-activation of both pathways. It has furthermore been shown that electrical auditory cortex burst stimulation exerts its effect predominantly on the extralemniscal medial geniculate body [24,25], which fires predominantly in burst mode [19,20]. These thalamic high-frequency burst discharges are particularly effective in activating large inhibitory postsynaptic potentials, whereas tonic firing is not [26], suggesting burst firing could be particularly effective in suppressing noise-like tinnitus. Thus, in summary, it was thought that burst stimulation of the auditory cortex might predominantly modulate the extralemniscal thalamus and could be particularly effective in suppressing thalamocortical hyperactivity syndromes via a nonlinear effect, which is more potent than tonic firing [14].

This knowledge was then translated to the pain pathways, based on similarities between tinnitus and pain, with regard to both anatomical pathways and physiological characteristics [27,28], as well as based on pathophysiological and clinical similarities [29–31]. This led to the first trial of burst stimulation on the spinal cord, in an attempt to modulate the medial pain pathways [7]. It was noticed that burst stimulation did not evoke paresthesia [7], which would permit placebo-controlled studies to be performed.

SCS: indications, results & limitations

During the end of the 1960s, SCS was developed as a treatment modality for medically intractable neuropathic pain. The original concept was based on the pain gate mechanism, which postulated that stimulation of large Aβ fibers suppresses pain transmission via the small unmyelinated C and small delta fibers. Its exact working mechanism has remained elusive, but most likely involves combination of a local spinal as well as supraspinal mechanism [32,33]. At the spinal level, both the ascending dorsal column fibers and the opioidergic [34] and serotoninergic [35] descending pain modulatory systems might be implicated in the pain-suppressing effect. As paresthesia are thought to be related to the activation of the large beta fibers [36,37], the targets of SCS mandates paresthesia, and paresthesia coverage has been used as a predictor for pain relief by SCS [38]. This precludes placebo-controlled studies to be performed [7], which has been considered the scientific Achilles heel of SCS.

SCS has been predominantly targeting limb pain in failed back surgery syndrome (FBSS) [39], but later evolutions demonstrated that SCS could be used for different kinds of pain, including refractory angina pain, severe ischemic limb pain secondary to peripheral vascular disease, peripheral neuropathic pain and chronic low-back pain, and that, in general, SCS was a safe and effective treatment for a variety of chronic neuropathic conditions [39]. Meta-analyses and systematic reviews indeed support the use of SCS for FBSS [40], critical limb ischemia [41], complex regional pain syndrome [42] and angina [43]. Even though long-term results are favorable to reoperation [44] or conventional pain management [45], not everybody responds to SCS and the results of SCS seem to decrease with time [46–48], resulting in a group of patients who are insufficiently helped by the SCS. After long-term stimulation (2–9 years), about 50% of patients still experience about 50% pain reduction [40,46,47]. Thus, a novel stimulation design that could improve results would be welcomed.

Working mechanism of burst technology

The exact working mechanism of the Prodigy is unknown except for the fact that source localized electroencephalography has demonstrated that in comparison to tonic stimulation, it exerts a similar effect on the lateral pain pathway, which is involved in encoding the discriminatory components of the pain (what, where and how intense is the pain stimulus). Burst technology, however, is capable of modulating the medial pain pathway in contrast to tonic stimulation, both clinically (as demonstrated by different effect in pain vigilance and awareness questionnaire) [8] and by its influence on the dorsal anterior cingulate cortex, demonstrated by source localized electroencephalography [8]. It was actually suggested that burst stimulation on the spinal cord exerts an effect that is reminiscent of cingulotomies performed for pain [8]. This selective routing of information via the medial pathway could be theoretically linked to a routing and multiplexing capacity of bursting [49].

But other mechanisms might be involved in burst stimulation as well. For example, it has been shown that there is a frequency-dependent opioid release in the dorsal horn with a maximal release at 500 Hz stimulation [50]. However, clinical evidence comparing 500 Hz tonic mode to 500 Hz burst mode shows that 500 Hz burst mode is superior to tonic mode. It is also possible that 500 Hz has a selective effect on Aβ fibers, similarly to what has been described for 2000 Hz [51] and thereby has a maximal effect on the pain gate mechanism. Another potential explanation is that burst is just more powerful than tonic stimulation,
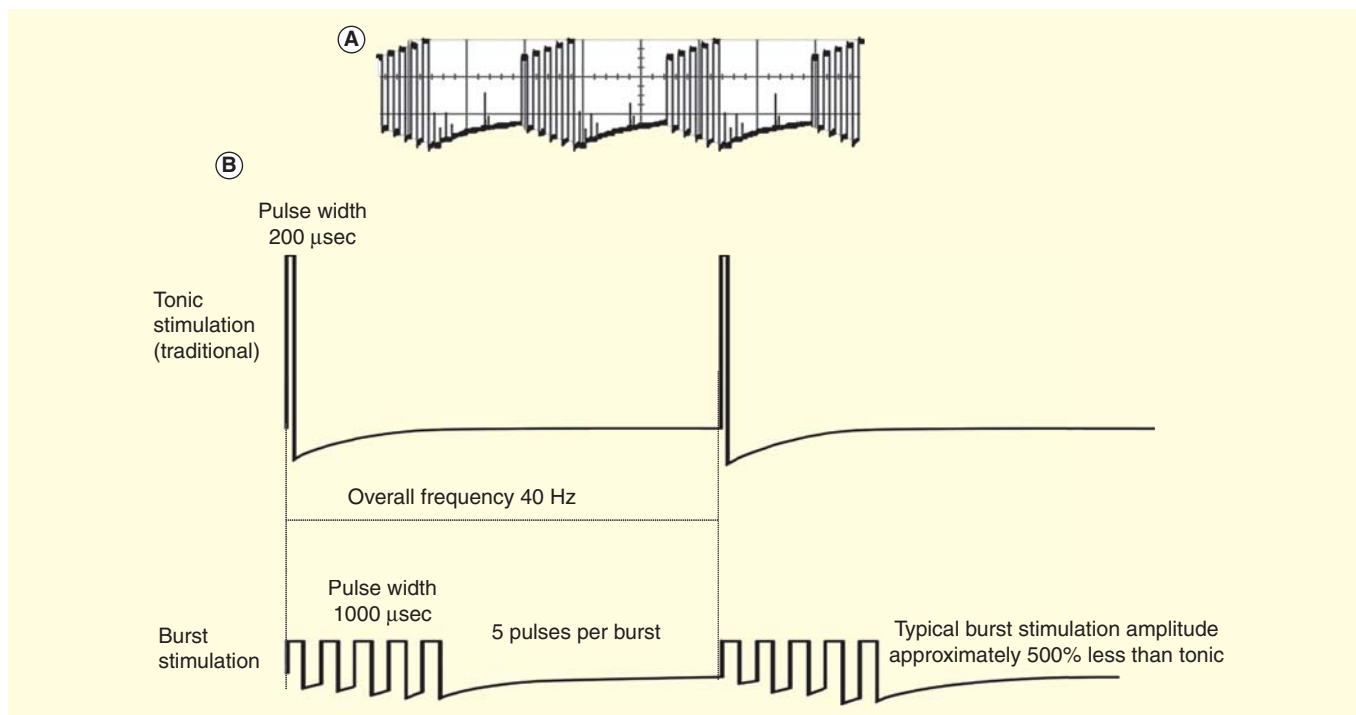
Table 2. The operation parameters of the Prodigy with burst technology.					
Parameter	Tonic range	Steps		Burst range	Steps
Pulse width	50–500 µs	Alternating 12 and 13 µs (starting with 12 µs)		50–1000 µs	50 µs
Frequency	2–200 Hz 200–500 Hz 500–1200 Hz	2 Hz 10 Hz 20 Hz			
Burst rate frequency				10–60 Hz	10 Hz
Intraburst frequency				250–500 Hz 500–1000 Hz	10 Hz 20 Hz
Amplitude	0–25.5 mA (max 12 V)	0.1–1.0 mA		0–12.75 mA	0.05–1.0 mA

Figure 2. Burst stimulation design. (A) Burst pattern as recorded from an oscilloscope. Five spikes of 1000 µs are delivered at 500 Hz, and this 40 times per second, that is, at 40 Hz **(B)** comparison of 40 Hz burst mode versus 40 Hz tonic stimulation mode.

both for excitatory [52,53] and inhibitory [26] postsynaptic modulation. Still another hypothetical working mechanism involves the selective activation of mixed electrical and chemical synapses at 500 Hz [54], permitting subthreshold oscillatory synchronization of functionally connected (via electrical gap junctions) areas [5]. Another potential working mechanism is that burst technology modulates the µ-opioidergic antinociceptive bursting descending pain modulatory pathways that activate the off cells and thereby prevent further pain signals from reaching the cortex. It is further possible that burst technology incorporated in the Prodigy system activates low-threshold tactile C-fibers, which have an antinociceptive function (Lu 2003, Delfini 2013, Vrontou 2013, Liljencrantz 2014).

Prodigy & regulation

Currently, the Prodigy only has a CE mark and is therefore available on the European market, as well as on markets that authorize its use when CE mark is obtained. There is no US FDA approval yet, but a non-inferiority study is currently being conducted for obtaining FDA approval.

Its current indications for use are:

1. For SCS, the Prodigy™ neurostimulation system is indicated as an aid in the management of chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS and intractable low back and leg pain.
2. For peripheral nerve stimulation of the occipital nerves, the Prodigy system is indicated as an aid in the management of the pain and disability for patients diagnosed with

intractable chronic migraine (15 or more days per month with headache lasting at least 4 h per day, failure of three or more preventative drugs and at least moderate disability determined using a validated migraine disability instrument [e.g., MIDAS or HIT-6]).

Cost–effectiveness of the Prodigy

In a recent poster presentation, it was shown that burst stimulation is cost–effective in comparison to tonic stimulation and conservative medical management. Based on the overall improvement on the response rate to the therapy, a decision model was created to predict the likely cost–effectiveness of this new stimulation pattern versus best medical treatment and tonic stimulation, and to conclude in which way this may change the use of SCS. In this study model, the budget impact of burst stimulation was calculated compared to classic tonic stimulation for FBSS. The overall result of this preliminary analysis showed that burst stimulation, by improving utility scores and by saving cost, could become a 'dominant' and first choice strategy for the treatment of FBSS [55].

Results of burst enabling technology outside the spinal cord

Burst stimulation has been used outside the spinal cord as well. As mentioned, it was first studied for tinnitus by electrodes implanted on the auditory cortex. Five patients with an electrode implanted on the auditory cortex were asked to rate their tinnitus distress and intensity on a visual analog scale before and after 40 Hz tonic and 40 Hz burst (five pulses at 500 Hz)

stimulation. All patients presented with both high-pitched pure tone and white noise components in their tinnitus. A significantly better suppression for narrowband noise tinnitus with burst stimulation in comparison with tonic stimulation ($Z = -2.03$, $p = 0.04$) was found. For pure tone tinnitus, no difference was found between tonic and burst stimulation ($Z = -0.58$, $p = 0.56$). No significant effect was obtained for stimulation amplitude ($Z = -1.21$, $p = 0.23$) and electrical charge per pulse ($Z = -0.67$, $p = 0.50$) between tonic and burst stimulation. The electrical current delivery per second was significantly different ($Z = -2.02$, $p = 0.04$) [14].

This was followed by an evaluation in a larger group of patients (n = 43) [15]. Thirty-seven percent of the patients responded to auditory cortex stimulation with tonic stimulation. Of the 63% who were non-responders, half benefited from burst stimulation. In total, 33% remained unaffected by the auditory cortex stimulation. The average tinnitus reduction was 53% for the entire group. Burst stimulation was capable of suppressing tinnitus in more patients and was better than tonic stimulation, especially for noise-like tinnitus. For pure tone tinnitus, there were no differences between the two stimulation designs. The average pure tone tinnitus improvement was 71 versus 37% for noise-like tinnitus and 29% for a combination of both pure tone and noise-like tinnitus [15]. It is of interest that the amount of people who could be rescued by burst stimulation for tinnitus [15] and pain [56] is similar (50–60%).

Burst stimulation has also been safely applied to the somatosensory cortex [10]. A patient who was successfully treated with somatosensory cortex stimulation for over 6 years for trigeminal anesthesia dolorosa associated with a subjectively malpositioned eye after multiple recurrent facial skin tumor removals developed new pain after more extensive surgery. Reprogramming the implanted electrode was unsuccessful. The presence of the electrode yielded too many artifacts on a renewed functional MRI; therefore, a PET scan was performed under evoked allodynia. Fusing the previous functional MRI with the new PET images depicted two novel targets for stimulation, one anterior and one posterior of the previous target and beyond the spatial configuration of the implant. After the addition of two new electrodes, the pain could again be controlled in a placebo-controlled way, but only when the two electrodes were activated in burst mode at 6 Hz burst mode and 500 Hz spike mode [10].

Burst stimulation has also been used for peripheral nerve stimulation for FBSS [9]. Following successful pain relief by transcutaneous electrical nerve stimulation of the occipital nerve, a subcutaneous electrode was implanted and three stimulation designs are tested: a classical tonic stimulation, consisting of 40 Hz stimulation, a placebo, and a burst stimulation, consisting of 40 Hz burst mode, with five spikes delivered at 500 Hz at 1000 μsec pulse width and 1000 μsec interspike interval. The patient's stimulation results demonstrated that burst mode was superior to placebo and tonic mode, and that the burst design was capable of suppressing both the least and worst pain effectively. She has remained almost pain free for over 3 years [9].

Figure 3. Prodigy with burst technology.
From the Clinician's Manual, reproduced with permission from St. Jude Medical Neurodivision, Plano, TX, USA.

Expert commentary & five-year view

In the near future, both new burst designs will be developed and novel indications will be studied with burst technology and the burst technology will become incorporated in more complex stimulators, capable of sensing and thus adaptive stimulation.

Considering the fact that burst firing is an intrinsic way of information transmission in the nervous system, burst stimulation seems to be a universally applicable stimulation design. Indeed, apart from the spinal cord [7,8], it has been applied off-label on the brain, more specifically on the auditory [14,15] and somatosensory [10] cortex, as well as on the cingulate gyrus [De Ridder D, Joos K, Vannneste S, 2014. Tinnitus As A Homeostatic Emotion: Anterior Cingulate Implants For Tinnitus, Submitted], the angular gyrus [13] and in peripheral nerve field stimulation [9].

Furthermore, as burst stimulations seems to modulate a multimodal salience network [57,58] it is to be expected that burst stimulation also has an effect on other pathologies, theoretically on all calcium T-channelopathies or all diseases characterized by bursting in the nervous system, the reason being that burst through its nonlinear wake-up call mechanism can override this pathological bursting. Diseases characterized by bursting that have already been treated consist of tinnitus [14,15] and multiple pain syndromes including myelopathic pain, diabetic neuropathic pain, phantom pain and anesthesia dolorosa as well as FBSS [7–9,59], and in a rare case report where a patient developed a reversible and controllable out-of-body experience caused by burst stimulation of the angular gyrus [13].

Based on this apparent universality, both anatomically and clinically, burst stimulation would make theoretical sense in the following pathologies as they are characterized by burst firing: Parkinson's disease in globus pallidus and subthalamic nucleus (Magnin, 2000; Piallat, 2011), other movement disorders (Magarinos-Ascone, 2008), obsessive–compulsive disorders in subthalamic nucleus (Piallat, 2011), depression in ventral tegmentum area (Friedman, 2008) and locus coeruleus

(Simson, 1988), schizophrenia (Vukanidovic, 2012), epilepsy (Sanabria, 2001; Beck, 2008; Cain, 2012), acute and chronic stress (Okuhara, 1999; Pavcovich, 1990; Mana, 1997), post-traumatic stress disorder and addiction.

The Prodigy system is a Gaudian internal pulse generator that tries to mimic nature by being as physiological as possible, heralding a new approach in neuromodulation. It is versatile enough to create specific waveforms for the different burst firing patterns that exist in our complex nervous system. It should be considered a first small step, only concerned with the output stage in a wider strategy, in a series of innovative technologies that will increase the integration of electronics and human nervous tissue as a brain computer interface ultimately leading to a neurointegrator, which can sense, process and integrate activity, ultimately becoming part of the nervous system, capable of replacing broken or dysfunctional units of neural processing.

Key issues

- Burst stimulation mimics burst firing in the nervous system.
- Burst firing has different characteristics than tonic firing
  - It is more powerful in eliciting both inhibitory postsynaptic potential and excitatory postsynaptic potential
    - Burst firing has a nonlinear build-up of the inhibitory postsynaptic potential and excitatory postsynaptic potential
    - It has a higher signal to noise ratio
  - Burst firing can route and multiplex information selectively
    - The medial (affective/motivational) pathway fires in burst mode
    - Burst firing is electrophysiological correlate of motivational salience
- Chronic pain arises when myelinated fibers are damaged resulting in spontaneous burst firing in C-fibers, thereby activating salience network (dACC + insula), generating pain and unpleasantness.
- This results in an urging for action via activation of the sympathetic system, which suppresses the antinociceptive system, causing the pain to remain present and become chronic as long as bursting continues.
- Treatment can be developed by silencing bursting – this is only possible by using burst stimulation.
- Bursts have a nonlinear build-up, that is, are stronger activator of inhibitory postsynaptic potential or excitatory postsynaptic potential and can route stimuli to medial pain system, thereby removing salience from pain, and thus attention to pain as well as unpleasantness.

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