Burst stimulation for pain suppression

8 - 5 - 3

Dirk De Ridder

Patented Burst stimulation

Brain Research consortium for Advanced Innovative & Interdisciplinary Neuromodulation
We should construct IPG’s that imitate the brain as they will be more powerful and less energy consuming.

L’architecte du futur construira en imitant la nature, parce que c’est la plus rationnelle, durable et économique des méthodes.
Mechanism of detecting change in environment

Burst firing

1. Burst mode is signal detector (wake-up call for change), tonic is feature detector (transmits content of change) (Sherman 2001, Cooper 2006)

2. Is wake up call because of non-linear response (Lisman 1997, Sherman 2001)

3. Higher signal to noise (Sherman 2001)

4. Permits selective routing and multiplexing (Izhikevich 2000)

Philosophy of pleasure and pain

Epicurus (341-270 BC)
- Pursuit of pleasure and absence of pain is **purpose of life**, but without excesses (based on Plato and Aristotle and Democritus)
  - Ataraxia: peace and freedom from fear
  - Aponia: the absence of pain
- Happiness = pleasure - pain

Bentham (1748-1832)
- Utilitarianism: One has to maximize pleasure and minimize pain...

Not only purpose of life but also **mechanism of life**

“Nature has placed mankind under the governance of two sovereign masters, pain and pleasure.”
Pain as a homeostatic emotion*

*Craig 2003
Ascending Bottom up Nociceptive

Descending Top down Anti-nociceptive

Fields 2004

Bingel 2008

Kong 2010
Lateral & medial SS system

**Lateral system** *(pain percept)*
- **WDR neurons** *(Price 2002)*
- **Firing in tonic** *(Lopez Garcia 1994)*
- **In lamina I and VI-VI** *(Willis 2001, 2002)*
- **Parvalbumin positive** *(Rausell 1992)*

**Medial system** *(affective/attentional)*
- **NS (nociceptive specific neurons)** *(Craig 1995)*
- **Firing in burst** *(Lopez Garcia 1994)*
- **In lamina I** *(Price 1979, Bernard 1989, 1990)*
- **To MDvc – Vmpo** *(Craig 1995, 2002)*
- **Calbindin positive** *(Blomqvist 2000)*

Kulkarni 2005

Kulkarni 2005
µ-opioid anti-nociceptive system

µ-opioid antinociceptive system bursts
When painful stimulus arrives On-cells are active transmitting pain stimulus to brain via ascending system

When pain is not more necessary Off-cells burst to suppress pain transmission

In other words, bursts signify beginning and end of pain stimulus, and end is associated with active µ-opioid mediated pain suppression

Burst also activates reticular nucleus of thalamus, blocking further input (Steriade 2000)
Bursts in ascending & descending pain pathways

Burst = electrophysiological mechanism for **detecting potentially harmful changes in the environment**. It thereby triggers emotion-based **attentional priority mode for perceptual processing of salient** (=behaviorly relevant) potentially harmful stimuli (wake up call).

Pain should be related to burst firing
Physiological pain suppression should be related to burst firing

De Ridder 2013
Bursts and neuropathic pain

Neuropathic pain


Firing in burst mode (Wu 2002)

Related to hyperalgesia (Wu 2002)
Translate this to neurostimulation
To burst or not in pain?
Pain & paresthesias

Neuropathic pain
Ectopic or spontaneous (Wu 2002) discharges in C fibres

Paresthesia and dysesthesia
Ectopic discharges in Aβ fibres (Ochoa 1980, Nordin 1984)
Neurostimulation

Spinal cord stimulation
Activates Aβ to suppress C and Aδ fibers
Via inhibitory interneurons (Melzack & Wall 1965)
Spinal cord stimulation

**Burst stimulation**
- Non linear response
- Stronger activator of cortex
- Might modulate burst firing medial and tonic firing lateral system

**Tonic stimulation**
- Might modulate tonic firing lateral system
Burst Spinal Cord Stimulation: Toward Paresthesia-Free Pain Suppression

INTRODUCTION: Spinal cord stimulation is commonly used for neuropathic pain modulation. The major side effect is the onset of paresthesia. The authors describe a new stimulation design that suppresses pain as well as, or even better than, the currently used stimulation, but without creating paresthesia.

METHODS: A spinal cord electrode (Lamitrode) for neuropathic pain was implanted in 12 patients via laminectomy: 4 at the C2 level and 7 at the T8–T9 level for cervicobrachialgia and lumboischialgia, respectively (1 at T11 at another center). During external stimulation, the patients received the classic tonic stimulation (40 or 50 Hz) and the new burst stimulation (40 Hz burst with 5 spikes at 500 Hz per burst).

RESULTS: Pain scores were measured using a visual analog scale and the McGill Short Form preoperatively and during tonic and burst stimulation. Paresthesia was scored as present or not present. Burst stimulation was significantly better for pain suppression, by both the visual analog scale score and the McGill Short Form score. Paresthesia was present in 92% of patients during tonic stimulation, and in only 17% during burst stimulation. Average follow-up was 20.5 months.

CONCLUSION: The authors present a new method of spinal cord stimulation using bursts that suppress neuropathic pain without the mandatory paresthesia. Pain suppression seems as good as or potentially better than that achieved with the currently used stimulation. Average follow-up after nearly 2 years (20.5 months) suggests that this stimulation design is stable.

KEY WORDS: Burst, Pain, Paresthesia, Spinal cord stimulation, Tonic

Results

**Tonic** stimulation : paresthesias in 91.7%

**Burst** stimulation : paresthesias in 17%

$\chi^2(12) = 6.13, p < .01$

$\chi^2 (12) = 0, p = 1$
Burst stimulation

Equal or better pain suppression (p<0.05)
   For back and limb pain
   For sensory and affective components

Higher current delivery per second
   130.8 mA versus 47.7 mA (p<0.02)
   Electrical charge per pulse is same
   Amplitude is lower for burst (0.6 vs 3.1 mA) (p<0.007)
   High pulse width (1000 µs)

De Ridder 2010
Placebo controlled study (n=15)
## Burst placebo controlled (n=15)

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De Ridder 2013
How much paresthesias do you have as a consequence of stimulation?

- Placebo Tonic Burst
- Visual Analogue Scale

\( F = 3.97, p < .05 \)

De Ridder 2013
 Improvement VAS

(F = 4.32, p < .05)

(F = 3.74, p < .10)

(F = 6.60, p < .05)

De Ridder 2013
Improvement PVAQ

\((F = 5.32, p < .05)\)

\((F = 4.01, p < .05)\)

_attention to pain_

_attention to changes in pain_

De Ridder 2013
Burst vs tonic stimulation

H°: Burst mediated multiplexing of medial pain pathway
Tonic stimulation in fMRI

Especially thalamus (GABAergic, Moens 2012) & SSC, but also little in insula caudate, PHC, hypothalamus

Rostral anterior cingulate cortex ~ pain relief ($R^2 = 0.13201$)
So is it really better?

Placebo-controlled study
   Not for limb pain
   For back pain
   For catastrophizing

Current stimulation centers
   Dusseldorf, Enschede, Oosterhuis,
   Leeds, Uppsala, Helsinki, Antwerp
   CRPS study
Is burst self-fulfilling prophecy?
Single center study (Enschede, The Netherlands)
Dr Lenders, Dr De Vos

What pathology?
Burst vs tonic SCS

All patients

Stimulation has significant pain suppressing effect ($F = 66.3; p < .001$)
Burst better than tonic
   Tonic 37% pain suppression
   Burst 52%

Pain suppression depends on etiology ($F = 18.3, p < .001$)

Best for PDN
   60% with tonic ($t = 5.45, p < .001$)
   77% with burst ($t = 9.00, p < .001$)
   Burst > tonic ($t = 2.99, p < .05$)

Good for FBSS
   40% with tonic ($t = 6.36, p < .001$)
   57% with burst ($t = 10.1, p < .001$)
   Burst > tonic ($t = 3.18, p < .01$)

Poor for not classified group
   10% with tonic ($t = 3.20, p < .01$)
   22% with burst ($t = 2.63, p < .05$)

De Vos 2014
Two-center study (N=102): Antwerp - Enschede

Can we rescue failures and further improve responders?
Can we rescue failures and further improve responders?
Total: Legs: $t = 4.66, \ p < .001$ & Back: $t = 3.94, \ p < .001$
Belgium: Legs: $t = 3.01, \ p < .01$ & Back: $t = 3.00, \ p < .01$
The Netherlands: Legs: $t = 3.53, \ p = .001$ & Back: $t = 2.64, \ p = .01$

De Ridder, in press
Two-center study (Sweden & Finland) (n=79)
Dr Walstedt, Dr Sulkko

How many prefer tonic, how many burst?
How many prefer burst?

N=79, 40 Sweden, 39 Finland
All were on tonic
Switch to burst
Sweden: 20% back to tonic
Finland: 28% back to tonic
Germany: 80% prefer burst
Antwerp: 80% prefer burst

Reasons:
Want paresthesias
No control over intensity of stimulation
Feels not nice
Not as good as tonic
Not better for pure back pain in Sweden

![Graph showing preference for burst stimulation in Sweden and Finland](image-url)
But...

What is important for paresthesia free SCS?

- Burst frequency? no
- Spike frequency? yes
- Pulse width? yes
- Interspike interval?
- Number of pulses (3, 5, 7)? yes
- Charge? yes
Burst spinal cord stimulation

Hypothetical working mechanisms

1. Burst firing like high frequency firing selectively modulates $\text{A}_\beta$ fibers, without activating $\text{C}$ fibers (Koga 2005, Sundar 2006)
   Subthreshold stimulation can already suppress pain

2. Frequency dependent opioid release from dorsal horn neurons with maximal release at 500 Hz (Song 2003)

3. Burst modulates medial and lateral system vs tonic only lateral system
   Spike number dependent selective synaptic transmission (Izhikevich 2003, Krahe 2004)

4. Burst modulates Off-cells of descending antinociceptive system

5. Burst is stronger activator than tonic

6. ...
Why 500 Hz?

Mimick nature
Because it has a maximal postsynaptic effect (Kim 1998)

What if we extend the line, would 1000 Hz spike rate still be better?
No! 1000 Hz burst is not better than 500 Hz burst (Van Havenbergh, in process)

And what about 10,000 Hz
Just a plateau? Or other unknown effects?
10,000 Hz x 30 μs x 1.6 mA = 0.48 C
500 Hz x 1000 μs x 1 mA = 0.5 C
1000 Hz x 500 μs x 1 mA = 0.5 C
Is it the burst or the 500 Hz frequency?

Burst (500 Hz spike mode) has lower motor threshold than
- 40 Hz tonic firing (Tang 2013)
- 500 Hz tonic firing (Gao 2010, Tang 2013)

Thus 500 Hz burst differs from 500 Hz tonic firing

As demonstrated clinically (Schu NANS 2013)
- N = 20, 500 Hz tonic vs burst@500 Hz vs placebo
- Burst for pain suppression
- 80% prefer burst
Burst spinal cord stimulation

Pulse duration

**Rheobase**: minimum current required to stimulate a neural element with a long pulse width

**Chronaxie**: pulse duration needed to evoke twice the rheobase current

- Chronaxie of myelinated **axons is 30–200 μs** (Ranck 1975)
- Chronaxies of **cell bodies and dendrites are 1–10 ms** (Ranck 1975)

Thus normal neurostimulation activates axons (Kringelbach 2007)

In burst dendrites and cell soma of Aβ fibers are hypothetically targetted (PW = 1 ms) rather than axons in the dorsal columns

Kringelbach 2007
Pulse width

PW > 500 µs decrease pinch evoked firing rate
  - 500 µs: 15% decrease
  - 750 µs: 24% decrease
  - 1000 µs: 49% decrease

PW < 500 µs increase pinch evoked firing rate
Conclusion

1. Burst stimulation mimicks nature, is as physiological as possible
2. Burst stimulation permits paresthesia free SCS
   but more importantly
3. Burst modulates affective & attentional component of pain
4. Targets the medial pain system = non-specific salience network
5. Probably the reason why people prefer burst (80%)(Sweden, Finland, the Netherlands, Germany and Belgium)
6. The more neuropathic the pain the better suppression
7. Burst SCS is better than placebo for all pain measures (back, limb & global pain)
8. Seems more powerful than tonic for limb and back pain
9. At the cost of increased energy consumption
10. Not just for SCS but for all CNS areas targeted (AC, SSC, ACC, DLPFC, TPJ, n Acc)
11. Thus is very likely universal
12. Frequency is less important than bursting
13. >500 Hz probably no extra benefit
Burst stimulation

Facts (published)

1. **Auditory cortex** for tinnitus (De Ridder 2009, 2011)
   - Rescues 48% of non-responders
   - Can suppress noise-like tinnitus in contrast to tonic stimulation
   - Improves tinnitus suppression in 50% from 24% to 53%

2. **Somatosensory cortex** for pain (De Ridder 2012)
   - Can rescue failure to tonic stimulation

3. **C2 stimulation** for FBSS (De Ridder 2013)
   - Burst significantly better than tonic (placebo controlled)

4. **TPJ in tinnitus** (De Ridder 2007)
   - Only 40 Hz burst stimulation induces out of body experience

5. **SCS for pain** (De Ridder 2010, 2013)
   - Is better for global pain than tonic
   - Is paresthesia free
   - Has very marked effect on attention to pain (mimicking frontal lobotomy)
   - 80% prefer burst (Schu 2013)
Other pathologies?

Already published data relate to synchronous bursting (Rinaldi 1991) in thalamocortical dysrhythmia pathologies (Llinas 1999)

1. SCS (De Ridder 2010, 2013)
2. Auditory cortex (De Ridder 2010)
3. Somatosensory cortex bursts (De Ridder 2013)
4. C2 stimulation (De Ridder 2013)

Theoretically sensible in other bursting pathologies

1. Parkinson’s disease in GPI and STN (Magnin 2000, Piallat 2011)
2. Other movement disorders (Magarinos-Ascone 2008)
3. OCD in STN (Piallat 2011)
4. Depression in VTA (Friedman 2008) and locus coeruleus (Simson 1988)
5. Schizophrenia (Vukanidovic 2012)
8. ...