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PERSPECTIVE

Visions on the future of medical devices in spinal cord stimulation: what medical device is needed?

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SUMMARY
Recently burst stimulation and 10 kHz stimulation have been developed as novel stimulation designs. Both appear to be superior to classical tonic stimulation in the amount of responders and the amount of pain suppression and have as an extra advantage that they are paresthesia-free. This evolution is very important as it shifts the focus of research from better targeting by developing new lead configurations to better communication with the nervous system. It can be envisioned that this is only the start of a new trend in spinal cord, brain, and peripheral nerve stimulation and that more new stimulation designs will be developed in the near future such as pseudorandom burst stimulation, pleasure stimulation, noise stimulation and reconditioning stimulation. This evolution mandates a new approach in the development of internal pulse generators, and the most obvious approach is to develop an upgradable stimulator, on which new stimulation designs can be downloaded, analogous to the apps people download on their smartphones. This will create a shift from hardware driven products to software driven stimulators.

Introduction

Spinal cord stimulation (SCS) was developed some 50 years ago as a treatment for medically intractable chronic pain, predominantly targeting not only arachnoiditis, complex regional pain syndrome and failed back surgery syndrome [1], but also refractory angina [2], as well as in chronic critical limb ischemia [3]. SCS not only reduces pain, improves quality of life, reduces analgesic consumption, but also allows some patients to return to work with minimal side effects apart from paresthesias [4].

The original concept was based on the pain gate mechanism [5], which postulated that stimulation of large Aß fibers suppresses pain transmission through the small unmyelinated C and small delta fibers. And indeed, when larger myelinated fibers degenerate, the high-threshold unmyelinated C-fibers start firing spontaneously in rhythmic bursts, which are related to the pain [6,7]. The working mechanism of SCS has remained somewhat elusive, but most likely involves a combination of local spinal as well as supraspinal mechanisms [8,9]. At the spinal level, both the ascending dorsal column fibers, as well as the opioidergic [10], serotoninergic [11], and dopaminergic [12] descending pain modulatory systems might be implicated in the pain-suppressing effect.

The current neuromodulation devices, aka internal pulse generators (IPGs), use technology originally developed for pacemakers [13]. The pacemakers were adapted to stimulate nervous tissue, but were never specifically designed for it. The first IPGs were therefore using constant voltage (Medtronic) technology, whereas later developments were based on constant current delivery (St Jude Medical and Boston Scientific). But they all had in common that the IPGs delivered tonic pulses, charge-balanced (either passively- or actively-balanced with a counter charge) after each positive pulse. This leads to limited flexibility, as the only modifications that can be programed into the stimulation design are the contact polarity, pulse width, frequency, and amplitude. That is even more limited by the fact that in most devices the output power to each contact is the same, even though one IPG (Boston Scientific) is capable of delivering different power assignments for each contact, thereby improving flexibility.

Recently, the neuromodulation world has been challenged somewhat by the arrival of two new stimulation designs, high-frequency stimulation, aka 10 kHz

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stimulation [14,15], commercialized by Nevro, which is a form of tonic stimulation, and burst stimulation [16–18], commercialized in Europe and the rest of the world by St Jude Medical, but not yet approved in the USA.

Burst stimulation is currently the only stimulation design that is not tonic in nature, as it delivers multiple spikes, typically five in number, which are partially charge-balanced after each spike and passively charge-balanced at the end of the five spikes [17]. But both 10 kHz and burst stimulation caused a shift from former approaches, which were mainly based on improving targeting by the development of multi-column leads to stimulate the spinal cord, such as the five-column and three-column leads to improve communication with the spinal cord, brain, or peripheral nerves by changing the stimulation design.

Is there a problem?

It is likely that the future of neuromodulation is not restricted to better targeting, but also to development of ever more new stimulation designs, to better communication to the nervous system, whether brain, spinal cord, dorsal root ganglion (DRG), or peripheral nerve, 'to communicate to the brain in a language it understands'. In essence, the goal is to tune the therapy to the individual patient and their pain condition. This could create challenges for patients and payers. If every new stimulation design/language to communicate with the nervous system requires a newly designed IPG, it will become costly for health systems, as an explosion of new waveforms is expected as companies quickly attempt to follow in this emerging trend of new stimulation modes.

Is there a solution?

The purpose of this paper is to demonstrate where the future of medical devices lies or could be moving to, with a particular focus on the development of an upgradable neuromodulation device or IPG that can function as a generic neuromodulator and is capable of being uploaded by different apps, in this case new waveforms, such as burst stimulation. St. Jude Medical introduced the first of such devices, the Protégé™, and expects to launch Proclaim™ IPG, the former is FDA-approved and the latter is CE-marked. What is unique about these devices is that they are an upgradable or open platform. This represents a dramatic shift in philosophy, from one IPG for one purpose to a philosophy that reflects modern society upgradability. We all have smartphones, being upgraded almost every year with some new features,

and depending on what we need we upgrade our smartphones or not. And smartphones have apps, which make the phone very individualized, which is what current personalized medicine is striving for in personalized cancer treatment, personalized psychiatry, personalized cardiology, etc. [19–21]. Thus, it follows that personalized pain medicine is to follow once the technology is available to apply it.

The development of 10 kHz and burst stimulation changed the field of neuromodulation because of their paresthesia-free nature, and the demonstration that some of these new waveforms such as burst stimulation also modulate the medial pain pathway, that is, the motivational/affective/emotional component of the pain in contrast to traditional tonic waveforms [16]. The fact that both new stimulation designs can suppress pain better than classical tonic stimulation [14–18,22–25] opens up an avenue for even more new stimulation designs to be developed. Changing IPGs for trying to improve patient outcomes will lead to more surgery, with surgical and infectious risks and a financial heavy burden on society. Therefore, the medical device industry has no other choice than to follow the smartphone example: generate a generic implantable pulse generator and download new stimulation waveforms as apps, in other words, create an upgradeable IPG.

The advantages are both commercially and ethically:

1. Less surgery for the patient (no replacements of IPGs): the Hippocratic oath contains the notion of 'primum non nocere' (first do no harm), and being able to download a new waveform into a generic upgradable IPG prevents surgery, with its potential risks and complications appearing consistent with this oath [26].
2. In failures, it is possible to recall patients when a new upgrade is developed, without renewed surgery and the promise of salvaged therapy. This has been done before for both tinnitus and pain, in which patients with a failure to tonic stimulation were recalled, and with a custom-made programmer, the patient's IPG was updated to burst stimulation in a research setting, rescuing 50% unsuccessfully treated tinnitus patients with auditory cortex stimulation in burst modality [27]. Similarly, in SCS, failures to tonic stimulation were reprogrammed to burst with the same custom-made programmer, permitting to rescue more than 60% [22]. This clearly shows the feasibility of the concept of an upgradeable stimulator.

3. But the concept can be extended even further. In successfully treated patients, it is possible to recall patients when a new upgrade is developed, without renewed surgery to verify whether pain suppression can be further improved. The feasibility of this approach has been demonstrated before. Using the same custom-made programmer, patients with tinnitus were asked whether they wanted to trial a new waveform (burst) to verify if their tinnitus could be further improved, and in 50% of the patients this lead to a further amelioration. Similarly, in SCS, the same approach improved more than 90% of the patients who were having benefit from tonic SCS and this was clinically relevant, with an improvement of approximately 25%, from 50% pain suppression to 74% pain suppression [22].

4. Another advantage of the upgradeable system could be that it leads to a higher acceptability of SCS if patients are convinced of the flexibility of system: the fact that the SCS could, in the future, become individualized or adapted to the individual can make this treatment modality more acceptable to the wider public, avoiding the common concept of 'buyer's remorse', which accompanies a significant decision only to find that a newer and better product becomes available after the decision is made, leaving them with the antiquated, less capable system. Indeed, a one-size-fits-all approach is somewhat outdated in modern times of tailored information transmission, as exemplified by the individual publicity companies like Google deliver.

5. Furthermore, it is cheaper to make one IPG than multiple and different ones for each waveform: also, from a commercial point of view, it would be prohibitively expensive to develop a new IPG for each waveform that might become available.

6. Furthermore, the upgradable IPG will permit faster evolution if only software needs to be changed rather than hardware. This is especially important in an age where the big pharma industry is dis-investing in the development of new neuropharmacological medication [28]. Central nervous system (CNS) disorders carry an enormous economic burden, >$2 trillion in USA and EU, which generates $80 billion/year for the pharma industry. The problem is that developing medication for CNS has 50% less chance of making it to the market and costs 30% more than heart medication. Knowing that 85% of drugs never reach the market results in the fact that no new medication is being developed for brain-related diseases, because it is too expensive, in view of the situation that four out of five medications fail phase III trials. Therefore, the big pharma industry is not interested anymore in drug development for CNS disorders. Since 2011, GSK, AstraZeneca, and Novartis have announced closures of neuroscience divisions globally, and Pfizer, Sanofi, Janssen, and Merck have begun to significantly downsize CNS operations [28]. This gap in new neuropharmacological developments can be filled in by out-licensing [28] and by the development of new stimulation approaches. An example is the development of burst stimulation, which was originally developed for tinnitus suppression by auditory cortex stimulation [27,29], and later translated to the spinal cord for pain, as well as to the peripheral nervous system for pain and tinnitus, [30,31] and is now being tested for anterior cingulate stimulation in the treatment of alcohol addiction (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366816). Thus, an upgradable IPG might extend its indications to cortex stimulation, deep brain stimulation (DBS), DRG stimulation, and peripheral nerve stimulation, considering that some of these new waveforms will be universally applicable [18].

Will there be any disadvantages linked to upgradable IPGs?

Even though there do not seem to be inherent disadvantages linked to upgradable IPGs, care should be taken on potential safety issues. The waveforms should fulfill safety requirements with regards to charge balancing, maximal charge delivery, ensuring new waveforms do not result in premature battery depletion, etc. Furthermore, the uploading should be protected against hacking, so that no waveforms are uploaded that could potentially harm the patient. This will be especially important if new stimulation designs are developed for reconditioning stimulation, where external stimuli are paired to electrical stimulation (see further). For improving safety neuromodulation can partially rely on what is being developed in the cardiac industry, where pacemaker industry, which currently is further advanced in its safety measures, can be copied and adjusted. And similarly the IPGs need to be protected against electromagnetic fields, a trend that is clearly in full development, with all major neuromodulation companies

developing MRI and thus electromagnetic field-compatible devices.

> It should, however, also be clear that an upgradable system will also have its limits and will, at a certain stage, also need to be upgraded. For example, when sensing will become available, permitting open and closed loop system designs, the current upgradable devices will need hardware changes implemented, requiring the upgradable IPGs to be upgraded themselves; in other words, they will need to be physically replaced.

Five-year view

If the future of SCS will rely on the development of upgradable IPGs, what are the new stimulation designs that can be expected, or that could benefit or improve the current state of SCS? In other words, what will SCS look like in 5 years, and can this be extended to brain stimulation, whether cortex or DBS?

What are the potential new future stimulation designs?

Modifications of burst stimulation [pseudo-randomness in time and/or place, more pleasurable stimulation (vs. simply pain suppression)]

Two new developments might involve modifications of rhythmic burst stimulation. One improvement could involve adding pseudo-randomness in the burst delivery, so that habituation can be prevented. This could be both in time as well as in space or combined in space and time. Pseudo-randomness in time means that the bursts in high frequency are presented in a pseudorandom way but at a specific frequency, as demonstrated in Figure 1. Basically, the interburst intervals vary in a random or pseudorandom way, but the amount of bursts and spikes does not change per second, meaning that both the burst and spike frequencies remain the same. Also, the poles of the electrodes from which the current is delivered remain the same.

In spatial pseudorandom burst stimulation (see Figure 2A), the poles that are activated change in a pseudorandom way, but the burst firing itself remains rhythmic. In combined temporal and spatial pseudorandom burst stimulation, the pseudo-randomness is a combination of both the above pseudorandom burst stimulation designs. It creates a maximal variability, which would be very important in preventing habituation to the stimulation, as well as preventing epilepsy in cortical stimulation.

A second modification could involve a sequential activation of adjacent poles of the electrode so as to induce an antinociceptive effect by selectively activating low-threshold tactile C-fibers (see Figure 2B). Basically, the stimulation design would mimic caressing the skin in an electronic form, thereby transmitting the pleasantness of tactile touch, [32,33] which is known to

Rhythmic burst stimulation

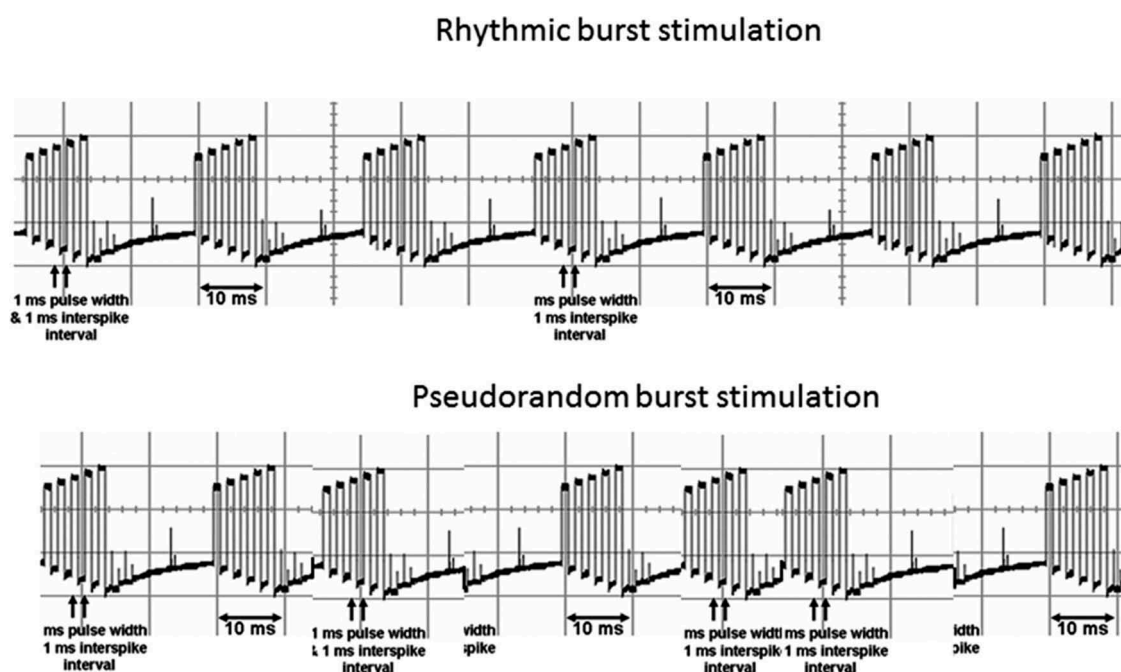## Pseudorandom burst stimulation

Figure 1. Pseudorandom burst stimulation (in time). The interburst interval is variable, but the amount of bursts within a second remains constant, i.e. the burst frequency remains constant, as does the spike frequency.

A

Concept
Run bursts randomly through different electrodes
prevent habituation
Can be limited to few electrodes for deep brain stimulation

R
A
N
D
O
M

B

Concept
Mimic caressing, gentle stroking, grooming
electronically, thereby creating pleasure sensation

Activate poles sequentially with 40 Hz bursts
from pole 1 to pole 8 on a subcutaneously
implanted electrode (or SCS or DRG) using bursts

Subthreshold for paresthesia

At a velocity of 1 to 10 cm/sec

Especially at C2 it should be powerful
(both peripherally and on SCS or dorsal root ganglion)
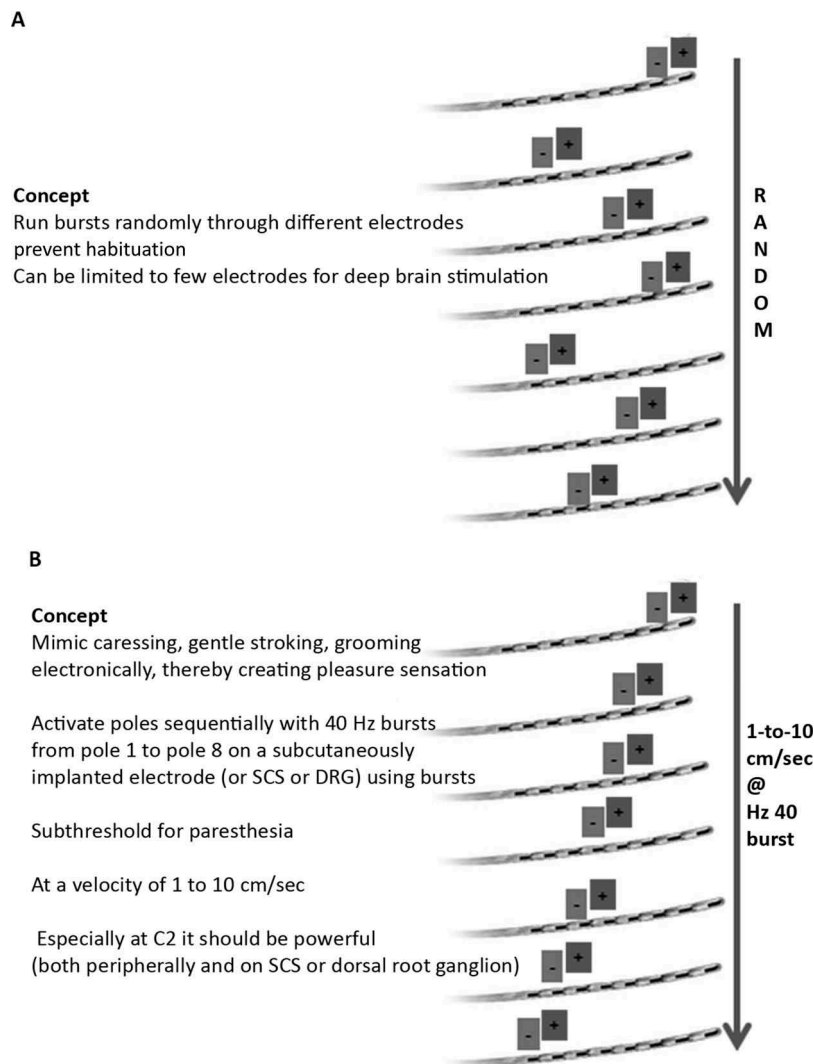
1-to-10
cm/sec
@
Hz 40
burst

Figure 2. (A) pseudorandom burst stimulation in space. The bursts are delivered from different poles of the electrode in a pseudorandom way, (B) pleasure stimulation: a sequential activation of the different poles of the electrode attempts to mimic caressing in an electronic form.

exert an antinociceptive effect [34,35]. Therefore, this stimulation design could be called pleasure stimulation.

Noise stimulation

An entirely new waveform could involve noise stimulation, which mimics the naturally occurring noisy structure of spontaneous electrical brain activity. In the brain at rest, this structure follows a $1/f^a$ pattern [36–39]. Analogous to the development of burst stimulation, the underlying concept of this waveform is to mimic physiological brain and nervous system activity [18]. Noise can have different structures, and the different structures are named by colors. White noise is characterized by the same power for all frequencies, whereas pink noise has a 1/f structure

in a log-log transformation, Brown(ian) noise a $1/f^2$, and black noise a $1/f^3$ structure (see Figure 3).

Noise itself has to be considered a signal that conveys information [40]. Advantages of noise in the nervous system are numerous, and include (1) stochastic resonance effect; (2) stabilization of a system; (3) creation of redundancy, which protects against mistakes or missing input; and (4) increase in the reliability of information transmission [41]. In summary, adding noise to a system permits adaptive stability (against over- and undershooting) while maintaining reliable information transmission [41]. Stochastic resonance is a phenomenon where a weak signal is detected or transmitted optimally in the presence of noise, that is, there is a paradoxical increase of output signal-to-noise ratio [40]. The basic prerequisite for a system to exhibit stochastic resonance is a threshold that needs to be exceeded in
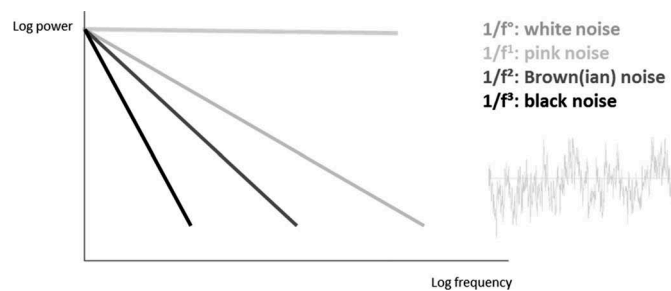
Figure 3. The colors of noise. Structured noise or $1/f^a$ noise. Depending on the slope, i.e. the 'a' in $1/f^a$ the noise is named by a different color.

order to activate the system [40]. When the signal in itself is not strong enough to exceed the threshold, small amounts of noise added either to the system or the signal may occasionally suffice to trigger activation [40]. Noise added to the somatosensory, [42,43] auditory, [44,45] and visual systems [46] (=stochastic resonance) improves signal detection, not only in the respective system but also in a cross-modal way [47]. Pink noise is better than white noise for obtaining a stochastic resonance effect [48,49].

Noise further stabilizes a system by providing the flexibility needed by cells to adapt to change, [50,51] and information transmission between complex systems is maximal in the condition of 1/f noise [52]. Thus, noise stimulation is ideal for conditions of degraded signal transmission, e.g. hearing loss, visual loss, hypoesthesia, etc., to improve signal transmission. For example, it has been shown that transcranial random noise electrical stimulation (tRNS) is better than direct current or alternating current stimulation in suppressing tinnitus, [53] which usually is related to hearing loss [54]. A case report has further shown that tRNS can improve neuropathic pain [55].

The feasibility of noise stimulation delivered through implanted electrodes has been tested using a DS8000 (World Precision Instruments, Sarasota, Fl, USA) digital stimulator and has shown that it can reduce tinnitus by applying pink noise stimulation on the auditory cortex and reduce pain by stimulation on the somatosensory cortex as well as on the spinal cord. It could further reduce spasticity by spinal cord noise stimulation (see Table 1). The scores in the table represent a numeric rating scale from 0 to 10 (0 = minimum or best score, 10 = maximum or worst score) obtained with burst stimulation (pre) and compared to noise stimulation (post).

Reconditioning stimulation

While noise stimulation carries information, the resultant effect is limited and cannot fundamentally

Table 1. First trials on spinal cord, auditory cortex, and somatosensory cortex with pink noise, alpha-modulated using a DS8000 digital stimulator. Prescores on a numeric rating scale from 0 to 10 (0 = minimum or best score, 10 = maximum or worst score) determine best scores obtained with burst stimulation, post best scores obtained with pink noise stimulation.

	Pre	Post
SCS spasticity	6	4
SCS pain	6	4
SSCS pain	5.5	3.5
ACS tinnitus	5.5	3

SCS: spinal cord stimulation, ACS: auditory cortex stimulation, SSCS: somatosensory cortex stimulation.

impact behavior. Alternatively, reconditioning stimulation is a new concept based on the fact that it should theoretically be possible to recondition the brain through paired stimulation of external stimuli with electrical stimulation of the reward system, thereby rewarding certain stimuli and/or disrewarding other stimuli. For example, tinnitus and neuropathic pain can be seen as a paradoxical salience (i.e. behavioral relevance) attached to the tinnitus sound or pain stimulus [56], thereby preventing habituation to the phantom sound or pain, as the sound is constantly kept conscious because it is considered behaviorally relevant [56]. Indeed, in both pain [57] and sound [58] stimuli, perception of the stimuli depends on the simultaneous co-activation of the salience network (dorsal anterior cingulate cortex and anterior insula) [59], and during meditation the suppression of the salience network correlates with an absence [60] or decrease [61] in pain perception of painful stimuli. Furthermore, consciousness itself critically depends on the functional connectivity strength of the dorsal anterior cingulate cortex and insula, i.e. the salience network [62]. Acute pain onset (aversion) results in negative activity change in the nucleus accumbens and pain offset (relief) produces positive activity change in the dorsal anterior cingulate cortex and nucleus accumbens. These changes are analogous in humans and rat
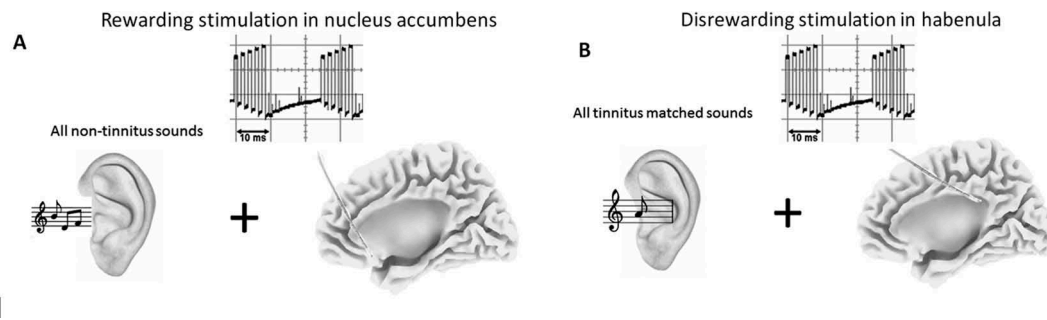
Figure 4. (A) pairing non-tinnitus sounds to rewarding stimulation in the nucleus accumbens could remove the paradoxical salience attached to the tinnitus sound, (B) pairing tinnitus sounds to disrewarding stimulation in the habenula could remove the paradoxical salience attached to the tinnitus sound.

[63,64]. However, in chronic low back pain, the nucleus accumbens response to acute pain is inversed in polarity, suggesting that the acute pain relieves the ongoing back pain [64]. Thus, the paradoxical predictive salience (of upcoming pain relief) attached to pain is encoded in the nucleus accumbens and could therefore theoretically be reconditioned.

It is theoretically conceivable that by pairing the non-tinnitus frequencies to a rewarding stimulation in the nucleus accumbens, the salience of the non-tinnitus sounds can be increased, and by not rewarding the tinnitus-matched frequencies the relative salience of the tinnitus-matched frequencies can be decreased (see Figure 4). Furthermore, a disrewarding stimulation in the habenula paired to the tinnitus-matched frequency could also remove the salience of the tinnitus tone. However, in order to develop reconditioning stimulation, waveforms need to be developed that give maximal reward by stimulating the nucleus accumbens or give maximal disreward by stimulating the habenula. A technique has been developed in animals based on self-stimulation that can discriminate which waveform or stimulation design rats prefer over others, thereby optimizing the waveform to the target [65].

designs that can tune therapy to a patient's individual condition. This will require the development of adjustable or upgradable IPGs, which will mimic the current evolution in smartphones, tablets, etc., in other words, a generic open-platform hardware will be required on which new stimulation designs can be downloaded, analogous to apps for smartphones. The Proclaim and the Protégé are the first real upgradable stimulator/IPGs, and set the tone for the future in developing medical devices for SCS and beyond. It is highly likely that DBS, cortex stimulation, and peripheral nerve stimulation, as well as DRG stimulation, will also benefit from this upgradable approach, as for example burst stimulation is also beneficial for cortex stimulation, both somatosensory cortex [66], auditory cortex [29], cingulate cortex [67] and peripheral nerve stimulation [30,31], and there is no reason to a priori believe the same rationale will not be applicable for DBS and DRG stimulation. The future is upgradeable.

Disclaimer

This manuscript was written without financial support from Saint Jude Medical, neurodivision, who developed the Protégé and Proclaim, the first commercially available upgradable IPGs.

Expert commentary and 5 year view

With the recent development of new stimulation designs such as burst stimulation [16–18,29] and high-frequency stimulation [14,15], it is clear that improvement of clinical results is not only to be found by better targeting or better coverage of paresthesias, but by the development of new stimulation

Financial & competing interests disclosure

D De Ridder has IP on the described stimulation designs. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- Recent new waveforms such as burst stimulation and 10 kHz stimulation demonstrate superiority to classical tonic SCS.
- Other new waveforms will be developed, such as pseudorandom burst (in time and space) stimulation, sequential burst stimulation, and noise stimulation
- New stimulation concepts, such as reconditioning stimulation, will also be developed.
- Developing new IPGs for every innovation is both clinically and financially undesirable.
- Therefore, upgradable IPGs need to be developed.
- The new waveforms and new stimulation concepts should be downloadable on the generic upgradable IPG.
- The Protégé and Proclaim are the first two examples of upgradable IPGs.
- The future of SCS will shift from hardware-based to software-based innovation
- The same evolution can be expected for deep brain stimulation, cortex stimulation, and peripheral nerve stimulation.

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