CHAPTER

14

Fundamentals of Burst Stimulation of the Spinal Cord and Brain

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OUTLINE

HISTORICAL CONTEXT OF BURST STIMULATION

The late Antoni Gaudi, Catalonia's most famous architect, stated that "the architect of the future shall construct by mimicking nature because it is a more rational, longer lasting, and more economical method (of building)." By applying the same philosophy to neuromodulation, it was proposed that mimicking different firing patterns that exist in the brain in an electronic way would be a rational way of performing neuromodulation (De Ridder et al., 2015b).

The nervous system uses at least two firing patterns to transmit information, tonic and burst firing (see Fig. 14.1), and these firing patterns can be regarded as either two languages or two different components of one language. The current implanted pulse generators are capable of delivering only tonic charge-balanced stimuli, mimicking tonic firing in the brain. However, some neurons can also fire in bursts, that is, using trains of high-frequency action potentials (APs) that occur during a plateau or active phase, followed by a period of relative quiescence, called the silent phase (Nunemaker and Satin, 2005). The plateau is generated by calcium influx via T channels, on which sodium spikes ride (Brumberg et al., 2000; Cain and Snutch, 2013; Jahnsen and Llinas, 1984).

Burst firing has some interesting neurophysiologic properties that might be beneficial for neuromodulation

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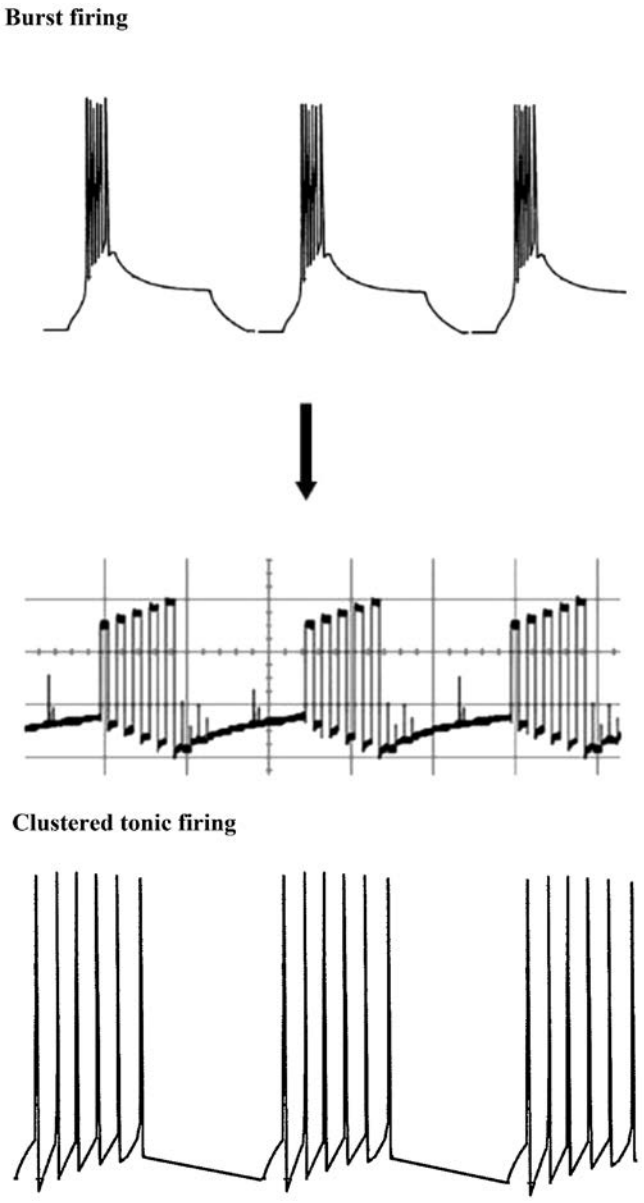

FIGURE 14.1 Burst firing (top) and clustered tonic firing. Note that burst firing rides on a plateau, whereas tonic firing does not. If tonic firing is intermittent, it can be called clustered tonic firing.

purposes. Burst stimulation has therefore been developed as a novel stimulation design that should be physiologically differentiated from clustered tonic stimulation, in which every pulse is immediately charge balanced (see Fig. 14.2).

WHAT IS SO SPECIAL ABOUT BURST FIRING IN THE BRAIN?

Burst firing can exert a strong positive (Swadlow and Gusev, 2001) or negative (Kim and McCormick, 1998) effect on postsynaptic responses that generates a larger excitatory or inhibitory postsynaptic potential than tonic stimulation. It has, therefore, been considered a wakeup call from the thalamus, signaling to the cortex that an important change has occurred in the sensory environment (Sherman, 2001b). Based on this idea, it had been suggested that burst firing is capable of overriding ongoing tonic firing (De Ridder et al., 2013a). This is intrinsically related to the high-frequency sodium spikes that ride on a calcium plateau, mediated by T-type calcium channels. The high-frequency, closely spaced spikes in a burst cause a nonlinear buildup of the postsynaptic APs, creating a kind of super-AP (Lisman, 1997; Sherman, 2001a,b).

Burst firing is characteristic of unmyelinated C-fibers, a bodywide system of salience (behavioral relevance)-detecting fibers, important in hedonic homeostasis. Behavioral relevance is achieved by adding weight to an external or internal stimulus, which phenomenologically is expressed as feelings of unpleasantness (mediated through high-threshold pain C-fibers) and pleasantness (Cabanac, 1992) (mediated through low- threshold tactile C-fibers) (Olausson et al., 2010) (Table 14.1). Behavioral relevance of the pain signal is processed by a group of brain areas that used to be called the pain matrix, but are now generally accepted as a multimodal (i.e., non–pain specific (auditory, visual, somatosensory, nociceptive system), salience network) (Legrain et al., 2011; Mouraux et al., 2011), encompassing the dorsal, anterior cingulate cortex, anterior insula, dorsomedial thalamus, amygdala, hypothalamus, and periaqueductal gray (Seeley et al., 2007). This network picks up behaviorally relevant changes that occur in the internal or external environment and signals its salience to the cortex via burst firing, whereas the content of the detected change is transmitted in parallel via the modality specific pathways in tonic mode (Sherman, 2001b).

Burst firing has some characteristics that help perform the task of a wakeup call. First, burst firing has a higher signal-to-noise ratio than tonic firing (Sherman, 2001a), and it permits selective routing and multiplexing of information via separate pathways (Izhikevich, 2000). Selective routing and multiplexing of information have been linked to recruitment of functionally connected areas through dendrodendritic transmission of subthreshold, calcium-mediated oscillations via gap junctions (Cain and Snutch, 2013) on which sodium spikes can subsequently ride. This creates synchrony in segregated spatially restricted but functionally connected areas (Cain and Snutch, 2013; Pereda, 2014).

The same burst of APs can be resonant for some neurons and nonresonant for others, depending on their natural frequencies (Izhikevich et al., 2003). Neither presynaptic nor postsynaptic neurons "choose" their frequencies "at will" but, instead, the frequencies are determined by the intrinsic properties of the neurons and the overall activity of the brain. Consequently, changing

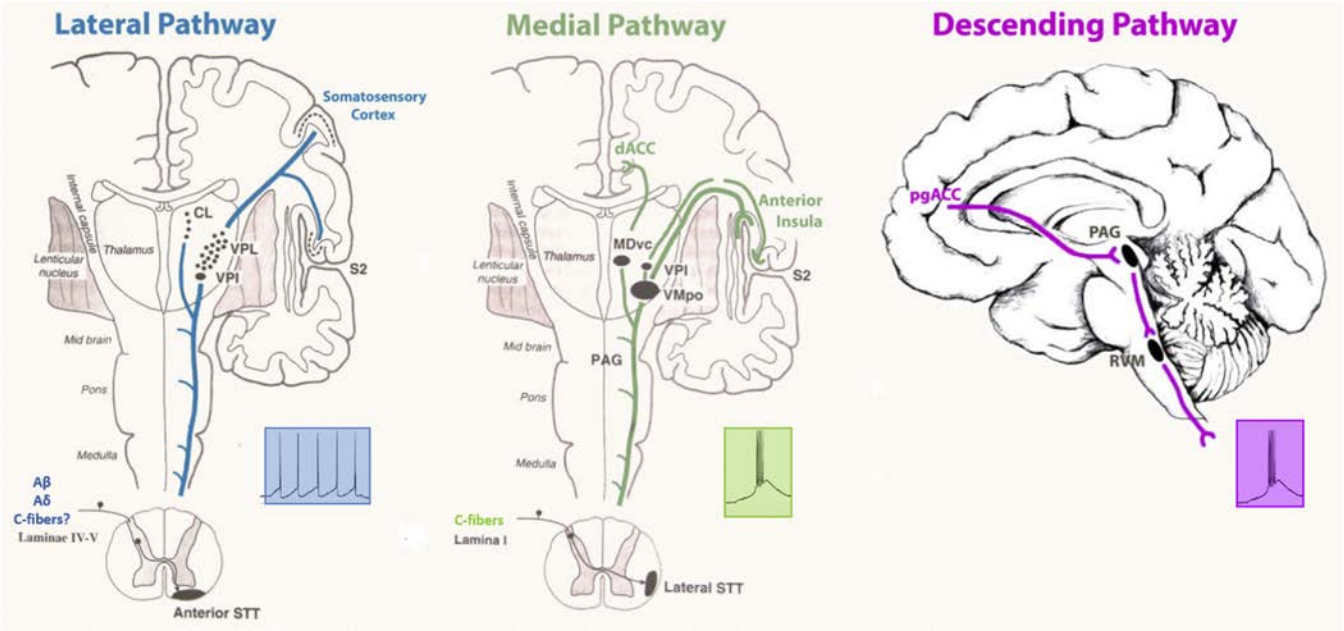

FIGURE 14.2 Two pain-provoking ascending pathways and one descending pain-inhibitory pathway involved in pain processing. *Figure modified from De Ridder, D., Vanneste, S., 2016a. Burst and tonic spinal cord stimulation: different and common brain mechanisms. Neuromodulation 19 (1), 47–59.* http://dx.doi.org/10.1111/ner.12368.

TABLE 14.1 Difference in Pain and Tactile Bursting Fibers, a Bodywide System of Motivational C-Fibers

	Pain C-Fibers	Tactile C-Fibers
Threshold	High (>2.5 mN)	Low (0.3–2.5 mN)
	Pinch, stab	Caress
Motivational capacity	Unpleasantness of pain	Pleasantness of caress
Location	Hairy and glabrous skin	Hairy skin, not genitals
Firing pattern	Burst	Burst
Cortical activation	Anterior cingulate, anterior insula	Posterior insula

the frequency content of bursts and subthreshold oscillations permits the brain to determine which areas communicate with each other at any particular moment. This mechanism allows the brain to reorganize itself dynamically within a few milliseconds, without changing synaptic hardware (Izhikevich et al., 2003). Furthermore, the amount of spikes within a burst might be important for the nonlinear buildup of the postsynaptic potential (the wakeup call), but it is of no importance for the selective routing of information, as a nonresonant synapse will be nonresonant regardless of the amount of spikes within a burst (Izhikevich et al., 2003).

Moreover, burst firing at a cellular level is related to phase-amplitude coupling (Sanders, 2016) (i.e., cross-frequency coupling (Jensen and Colgin, 2007), also known as nesting) at a macroscopic level. In the brain, lower

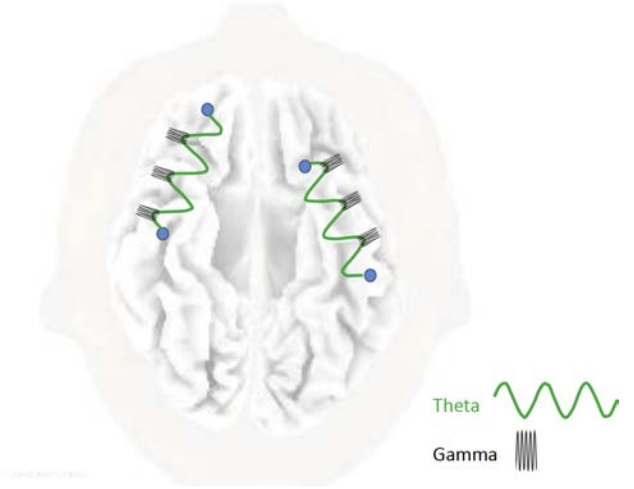

FIGURE 14.3 Amplitude-phase cross-frequency coupling: the phase of the lower frequency (δ, θ, α) is related to the amplitude of the higher frequency (β, γ). As such, the lower frequency functions as a carrier wave for the higher frequency.

oscillation frequencies such as δ (1–3 Hz), θ (4–7 Hz) or α (8–12 Hz) are transmitted over long distances, whereas higher frequencies such as β (12–30 Hz) or γ (>30 Hz) are limited to spatially restricted areas (von Stein and Sarnthein, 2000). In phase-amplitude cross-frequency coupling, the amplitude of the higher nested frequency (β, γ) is related to the phase of a lower frequency (δ, θ, and α) (Fig. 14.3). As such, the lower frequency functions as a carrier wave for the higher frequency (Varela et al., 2001). The information is encoded by the higher

frequency, which is broadcast throughout the brain by riding on the lower carrier frequency. Cross-frequency coupling is involved in attention (Voloh et al., 2015), emotion (Liu et al., 2015), cognition (Canolty et al., 2006), and disease states such as pain (Liu et al., 2015), tinnitus, Parkinson disease, depression, etc. (i.e., thalamocortical dysrhythmias) (De Ridder et al., 2015; Llinas et al., 1999).

BURST STIMULATION OF AUDITORY CORTEX FOR TINNITUS

Burst stimulation was initially developed to treat tinnitus via the implantation of electrodes overlying the primary and secondary auditory cortices. It was assumed that burst stimulation could suppress both tonic and burst firing due to its nonlinear buildup of APs (De Ridder et al., 2007a,b), whereas tonic stimulation is be able to suppress only tonic firing (except at high frequencies by creating neurophysiologic silence) (Beurrier et al., 2001).

With regard to tinnitus, it was hypothesized that noiselike tinnitus may be caused by increased burst firing in the nontonotopic (extralemniscal, nonspecific, salience) system, whereas pure tone tinnitus may be the result of increased tonic firing in the tonotopic (lemniscal, specific) system (De Ridder et al., 2007a,b). Narrow band tinnitus could be the result of a coactivation of both pathways.

When θ burst stimulation (Huang et al., 2005) was introduced as a novel form of transcranial magnetic stimulation (TMS), it was quickly applied to tinnitus as well (De Ridder et al., 2007a,b) and extended to α and β burst TMS (De Ridder et al., 2007b). Compatible with the hypothesis that noise-like tinnitus was the result of increased activity in the nontonotopic, extralemniscal system (which fires in burst mode), burst TMS of the secondary auditory cortex seemed capable of suppressing noise-like tinnitus significantly better than tonic TMS (De Ridder et al., 2007a,b). Concomitant with the TMS results, a custom-made program was developed capable of creating burst stimulation in a commercially available internal pulse generator, and tinnitus patients were implanted with extradural electrodes overlying the primary and secondary auditory cortices. In an initial study, it was shown that tonic stimulation could improve only pure tone tinnitus, not noise-like tinnitus (De Ridder et al., 2006).

To investigate the differential effect of burst stimulation compared with tonic stimulation, implanted tinnitus patients presenting intractable tinnitus to tonic stimulation were subsequently investigated by using burst auditory cortex stimulation (De Ridder et al., 2010b). Applying burst stimulation generated improvement for 48% of the tinnitus patients who did not respond to tonic stimulation (De Ridder et al., 2011b). Furthermore, 50% of patients who did respond to tonic stimulation obtained even more tinnitus reduction by switching to burst stimulation. In this group of responders to tonic stimulation, tinnitus suppression was 24% with tonic versus 53% for burst stimulation (De Ridder et al., 2011b). Therefore, adding burst stimulation improves auditory cortex stimulation for tinnitus from a poor response rate to an acceptable, though far from ideal, suppression rate (De Ridder et al., 2011b). Burst stimulation seems especially beneficial for patients with difficult-to-treat noise-like tinnitus (De Ridder et al., 2010b, 2011b).

BURST STIMULATION FOR PAIN

Pain can be defined as perception that encompasses painfulness (sensory component) and suffering (affective component). Physiologically, nociceptive pain (acute pain induced by activating nociceptors) can be considered as a protective sense against a harsh environment but loses this function and becomes independent of it in chronic neuropathic pain (Kandel, 1989), which is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system (Treede et al., 2008). The unpleasantness of pain is motivational in that it induces the animal/human to do something about the pain—to orient behavior to withdraw from the painful stimulus (fight or flight).

Pain is usually an aversive signal processed by at least three pathways: two, ascending, pain-evoking pathways (Bushnell et al., 2013; Price, 2000) and at least one, descending, pain-inhibitory pathway (Fields, 2004). The medial pain pathway encodes the motivational/affective component of pain (Bushnell et al., 2013; Price, 2000) (i.e., the unpleasantness) (Bushnell et al., 2013; Rainville et al., 1997), the lateral pathway encodes the discriminatory/sensory (Bushnell et al., 2013) component, and the descending pathway suppresses ongoing pain in a state-dependent manner (Fields, 2004). The ascending medial and lateral pain pathways are processed in parallel (Frot et al., 2008) and can be individually modified without affecting the other pathway (Bushnell et al., 2013). The ascending medial system is activated by C-fibers and connects to the mediodorsal and ventral, posterolateral nuclei of the thalamus, and from there, its connections, respectively, reach the anterior cingulate and anterior insula (Craig, 2002, 2004; Price, 2000). In fact, it is a nonspecific, salience pathway (Iannetti and Mouraux, 2010; Legrain et al., 2011; Mouraux et al., 2011), indicating the stimulus is behaviorally important. The medial pathway is activated not only by nociceptive stimuli but also by visual, auditory, and nonnociceptive somatosensory stimuli (Legrain et al., 2011). The ascending, lateral pain pathway is activated by C-, Aδ-, and Aβ-fibers and

connects to the ventral, posterolateral nuclei of the thalamus and from there reaches the somatosensory cortex and parietal area (Craig, 2002; Price, 2000). The descending pain inhibitory system involves the rostral and pregenual anterior cingulate cortex and connects to the periaqueductal gray, and from there is relayed further to the somatosensory periphery (Craig, 2002; Kong et al., 2010) (Fig. 14.2).

Based on the promising results in tinnitus, it has been hypothesized that pain could be the analogue of pure tone tinnitus and that paresthesias could be the analogue of noise-like tinnitus(De Ridder et al., 2011a; De Ridder and Van de Heyning, 2007). Based on the similarities between tinnitus and pain, the burst stimulation protocol was also applied to the somatosensory system, more specifically to the spinal cord and somatosensory cortex (De Ridder et al., 2015b).

Spinal cord stimulation (SCS) was developed more than 50 years ago as a novel treatment for medically intractable, chronic pain, targeting failed back surgery syndrome, arachnoiditis, and complex regional pain syndrome (Taylor, 2006), as well as chronic critical limb ischemia (Ubbink and Vermeulen, 2013) and refractory angina (Taylor et al., 2009). SCS not only reduces pain but also improves quality of life, reduces analgesia intake, and permits some patients to return to work, with minimal side effects apart from paresthesias (Mailis-Gagnon et al., 2004).

The original concept of SCS was based on the gate control theory of pain (Melzack and Wall, 1965), which postulated that stimulation of large Aβ-fibers can inhibit pain transmission via the small unmyelinated C-fibers and thinly myelinated Aδ-fibers. The working mechanism of action (MOA) of SCS has not been fully elucidated but very likely involves both a local effect and a combination of local spinal as well as supraspinal mechanisms (Barchini et al., 2012; Saade and Jabbur, 2008). At the spinal level, the ascending dorsal column fibers, as well as the opioidergic (Fields, 2004), serotoninergic (Song et al., 2009) and dopaminergic (Meyer et al., 2009) descending pain modulatory systems, might be implicated in the pain-suppressing effect of SCS. See Chapter 15 for a thorough discussion of the MOA of SCS.

Since the initial conception of the pain gate theory, it has been shown that when larger myelinated fibers degenerate, the high-threshold, unmyelinated, pain-transmitting C-fibers, but not the low-threshold, tactile C-fibers, start firing spontaneously in rhythmic bursts, which is related to the pain (Wu et al., 2001, 2002). Thus, it intuitively makes sense that electrically stimulating the remaining large Aβ-fibers might suppress this spontaneous, pain-related, rhythmic bursting.

The unique feature of burst technology is related to its fundamental aspect of mimicking nature, more specifically the burst firing pattern that exists in our nervous system from the periphery, to the autonomic nervous system, to the spinal cord, all the way up to the brain, both in the reward system and in the thalamocortical columns. By providing stimulation in a physiologic manner, burst stimulation permits paresthesia-free SCS (De Ridder et al., 2010b). Indeed, there is no reason why, in a physiologic way, paresthesia would have to be required to obtain pain suppression, as is the case with tonic stimulation (North et al., 1991).

The beauty of a paresthesia-free, stimulation experiment (as with burst SCS) is that 40 years after its inception (Shealy et al., 1967; Wall and Sweet, 1967), for the first time, a truly randomized, double-blinded, placebo-controlled study can be performed, comparing active SCS (no paresthesia) with sham SCS (no paresthesia) and finally demonstrating what every pain physician already knows—that SCS is better than placebo for all pain measures (back, limb, and global pain) (De Ridder et al., 2013a; Schu et al., 2013).

Whereas this paresthesia-free stimulation (Burst SCS) (De Ridder et al., 2010a, 2013a) might seem important for patient satisfaction, a recent study demonstrated that this was a reason to prefer burst technology over tonic stimulation for only 10% of patients (Courtney et al., 2015). What is more important for patient satisfaction is the fact that burst stimulation modulates the affective and attentional components of pain. This is demonstrated by the dramatic score differences in the pain vigilance and awareness questionnaire, which measures attention to pain and changes in pain, between patients in the burst SCS group and patients in the tonic SCS group (De Ridder et al., 2013a). Defocusing the patient's attention from pain is similar to what frontal lobotomies evoke (Freeman and Watts, 1948; Watts and Freeman, 1948). It is of interest that the area that burst stimuli modulates is the same area where cingulotomies (i.e., dorsal anterior cingulate cortex [dACC]) (De Ridder et al., 2010a) were and are performed (Wilkinson et al., 1999; Yen et al., 2009). This dACC area colocalizes with the area that encodes the unpleasantness of pain (Rainville et al., 1997), the behavioral relevance of pain (i.e., salience) (Seeley et al., 2007), and the emotional and suffering aspects of pain (Eisenberger, 2012). The dACC modulation by burst stimulation also significantly differs from the area that tonic stimulation modulates (De Ridder and Vanneste, 2016a). From an electrophysiologic point of view, burst SCS modulates the dACC (De Ridder and Vanneste, 2016a; De Ridder et al., 2010a), which is the end station of the medial pain system (Bushnell et al., 2013; Carlino et al., 2014; Craig, 2002; Fields, 2004; Price, 2000; Vogt, 2005) (Fig. 14.4, Table 14.2). This is most likely why 80–90% of people who are treated with both burst and tonic stimulation prefer burst stimulation (Courtney et al., 2015; de Vos et al., 2014; Schu et al., 2014).

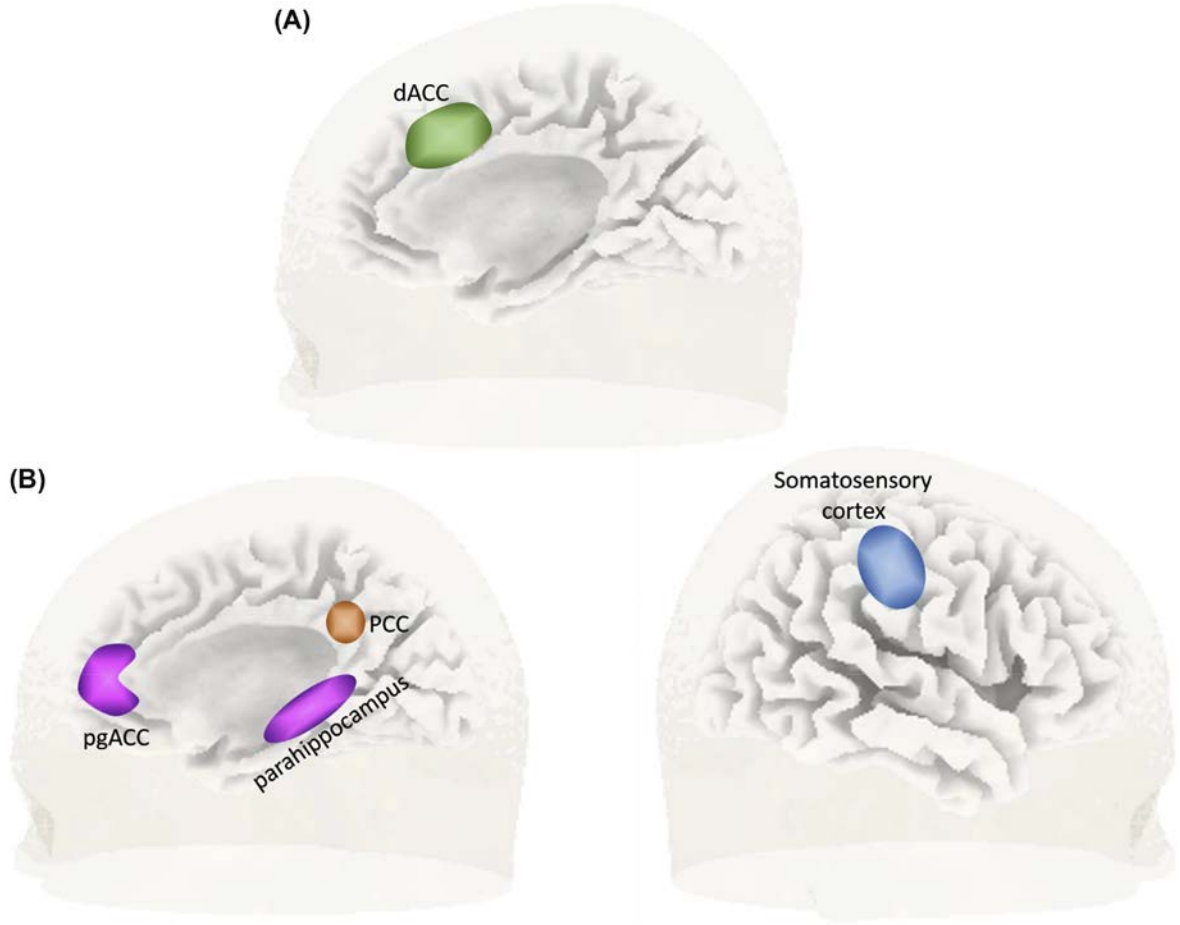

FIGURE 14.4 (A) Burst stimulation, in contrast to tonic stimulation, modulates the dorsal anterior cingulate cortex (dACC); that is, the medial pain pathway (green) (De Ridder and Vanneste, 2016a; De Ridder et al., 2010a). (B) Burst and tonic stimulation both modulate the descending pain inhibitory pathway, involving the pregenual anterior cingulate cortex (pgACC) and parahippocampus (purple), as well as the lateral pain pathway; that is, the somatosensory cortex (blue). Furthermore, both stimulation designs modulate the posterior cingulate cortex (PCC) (orange), which modulates the descending pain inhibitory pathway (Kucyi and Davis, 2015).

TABLE 14.2 Commonalities and Differences Between Burst and Tonic Stimulation.

Burst Stimulation	Tonic Stimulation
Descending pain inhibitory (pgACC, PHC)	Descending pain inhibitory
Lateral pain pathway (SSC)	Lateral pain pathway
Nonlinear stronger activator	
Medial pain pathway (rACC/DLPFC)	–
Rerouting/multiplexing	
Normalizes pain promoting/pain suppressing balance	Decreases pain promoting/pain suppressing balance
Dopamine?	GABA

DLPFC, *dorsolateral prefrontal cortex;* pgACC, *pregenual anterior cingulate cortex;* PHC, *parahippocampus;* rACC, *rostral anterior cingulate cortex;* SSC, *somatosensory cortex.*

For a similar amount of discriminatory/sensory pain suppression, the affective, attentional component of pain is better suppressed, so that patients do not care about their pain anymore; they can defocus from their pain. This is why, even if limb pain and back pain, in a placebo-controlled study, were not better suppressed by burst SCS than with tonic SCS, global pain was better suppressed with the burst technology (De Ridder et al., 2013a). Global pain perception can be seen as the combination of painfulness and suffering; that is, it combines the discriminatory/sensory component of pain (spatial, type, intensity) and the affective/motivational component of pain, whereas a visual analog scale or numeric rating scale of limb and back pain does not. It is important to note, however, that these initial results comparing burst SCS with tonic SCS were comparing results at very short time periods of stimulation (1–2 weeks), using different stimulation designs, and that, in longer follow-up periods, all measures become superior with burst

technology (De Ridder et al., 2014). The reason for this time course of difference is currently unknown, but it can be hypothesized that, through its attentional neglect for the pain, pain intensity also progressively decreases.

A study that more specifically looked at what kind of pain was better suppressed with burst technology demonstrated that neuropathic pain is better suppressed than failed back surgery pain (de Vos et al., 2014).

Another interesting finding is that increasing the frequency above 500-Hz spike mode does not seem to elicit a further improvement in pain suppression. Indeed, a study demonstrated that 500- and 1000-Hz burst stimulations do not significantly differ in pain suppression (Van Havenbergh et al., 2015), creating doubt as to the extra value of driving stimulation devices to very high frequency stimulation (Al-Kaisy et al., 2014). Indeed, in a study comparing burst SCS versus 10-kHz stimulation, back pain was equally well suppressed, and burst stimulation seemed to better suppress limb pain (Kinfe et al., 2016). Interestingly, burst and 10-kHz stimulations improve mood and sleep equally well (Kinfe et al., 2016).

WORKING MOA OF BURST STIMULATION

The exact working MOA of burst stimulation is incompletely unraveled. Theoretical assumptions based on the physiologic function of burst firing in both animal and human studies have proposed multiple, scientifically testable hypotheses and working MOAs, which are not mutually exclusive (Tables 14.2 and 14.3).

Source localized EEG functional imaging data (De Ridder et al., 2010a, 2013a) do strongly suggest that burst stimulation not only modulates the lateral and descending pain pathways but also has an influence on the medial pain pathway, as the dorsal part of the ACC is modulated by burst stimulation when contrasted to tonic stimulation. This extra modulation of the medial pain pathway by burst stimulation, while also modulating the descending, pain inhibitory and ascending, lateral pain pathway, is possibly due to the following MOAs:

1. Burst firing has routing and multiplexing capacities (Izhikevich et al., 2003).
2. Burst stimulation is a stronger activator (Sherman, 2001b; Swadlow and Gusev, 2001) and inhibitor (Kim and McCormick, 1998) of postsynaptic potentials than tonic stimulation.
3. The use of 500 Hz in the burst mode has a maximal inhibitory effect on the postsynaptic neuron (Kim and McCormick, 1998).
4. Burst firing, at 500 Hz, like high-frequency firing, could selectively modulate Aβ-fibers, without activating C-fibers (Koga et al., 2005; Sundar and Gonzalez-Cueto, 2006).
5. Burst stimulation modulates low-threshold, tactile C-fibers, which are known to be antinociceptive (Liljencrantz et al., 2014; Liljencrantz and Olausson, 2014).
6. Burst stimulation induces frequency-dependent opioid release from dorsal horn (DH) neurons with a maximal release at 500 Hz (Song and Marvizon, 2003).
7. Burst stimulation could modulate electrical gap junctions in the DH, which are known to be involved in the production of chronic pain (Wu et al., 2012), as burst firing can induce activity-dependent, long-term depression of these electrical synapses (Haas et al., 2011).

Looking for these alternative working MOAs is important as it is clear from animal research that burst stimulation does not exert its pain-inhibitory effect through GABAergic mechanisms, as does tonic simulation (Crosby et al., 2015a).

TABLE 14.3 Hypothetical Working Mechanisms of Burst Stimulation

Hypothetical Working Mechanisms of Burst Stimulation
1. Burst firing like high-frequency firing selectively modulates Aβ-fibers, without activating C-fibers
2. Frequency-dependent opioid release from dorsal horn neurons with maximal release at 500 Hz
3. Burst modulates medial and lateral system vs. tonic-only lateral system
4. Burst modulates off-cells of descending antinociceptive system
5. Burst is stronger activator than tonic
6. Activation of pleasure evoking tactile C-fibers
7. 500-Hz burst induces long term potentiation of mixed electrical and chemical synapses
8. Combination of the above

WHAT STIMULATION PARAMETERS ARE IMPORTANT FOR PAIN SUPPRESSION?

In contrast to tonic stimulation, the parameter space of burst stimulation is very large. Whereas for tonic stimulation, there are only three parameters that can be modified (frequency, pulse width, and amplitude, there are six parameters that can be adjusted for burst stimulation, creating both an unseen freedom of programming and a possible nightmare, if programming without knowledge.

Burst Frequency

For burst SCS, the default setting consists of 40-Hz burst mode, with five spikes at 500-Hz spike frequency, a pulse width of 1000 μs, and an interspike interval of

1000 μs, which is based on thalamic burst parameters. The 40-Hz burst mode is similar to the frequency that is most commonly used in tonic SCS. Whether burst frequency is important in humans is unknown. An animal pain model study of burst SCS did not find any significant differences in the effectiveness of burst SCS, either for the amount of responding neurons or in reduction of neuronal activity for different burst frequencies (Crosby et al., 2015b). However, whether this translates into clinical experience has yet to be determined.

Based on the principle that therapeutic burst stimulation should mimic physiologic burst firing patterns in the nervous system, it is conceivable that burst firing in different parts of the nervous system would require different parameters. For example, burst firing in the reward system and autonomic nervous system in humans is characterized by low-frequency bursts in the δ–θ frequency range (McAllen and Malpas, 1997; Zaehle et al., 2013). In clinical practice, burst stimulation at the cingulate gyrus (De Ridder et al., 2016a; De Ridder, Manning, et al., 2016) seems to be most efficacious at 6–10 Hz burst mode and at the primary somatosensory cortex at 4–8 Hz burst mode (De Ridder et al., 2013c), whereas burst stimulation at the posterior part of the superior temporal gyrus (i.e., secondary or tertiary auditory cortex) seems to be more variable (De Ridder et al., 2010b, 2011b). However, no systematic study has been undertaken to verify whether this assumption is correct.

Spike Frequency

An animal study has demonstrated that spike frequency is important in determining the amount of responsive neurons to burst SCS (Crosby et al., 2015b); however, spike frequency of burst SCS does not influence neuronal activity (Crosby et al., 2015b). 500 Hz is selected for the reasons discussed here. As mentioned, the burst-firing sodium spikes ride on a calcium-dependent plateau. The positive deflection of the plateau and positive spikes are charge balanced after all high-frequency spikes are terminated (i.e., at the end of the entire burst). This differentiates burst stimulation from high-frequency clustered tonic firing, in which all spikes within the burst are individually charge balanced. A recent study demonstrates that there is a clinical difference when comparing continuous 500-Hz subthreshold tonic mode with 500-Hz burst mode (Schu et al., 2013), demonstrating the importance of the burst waveform design for clinical efficacy.

Pulse Width

In contrast to activating axons, which can be accomplished by using pulse widths of up to 300 μs, a 1000-μs pulse width is required if the aim is to be as physiologic as possible (i.e., to activate dendrites and cell bodies) (Ranck, 1975). In a recent animal study, it was shown that there exists a pulse width–dependent suppression of pinch evoked firing rates. Pulse widths of <500 μs increased pinch evoked firing, whereas pulse widths of >500 μs decreased pinch evoked firing rates. Pulse widths of 500 μs resulted in a 15% decrease of pinch evoked firing rate, whereas pulse widths of 750 and 1000 μs produced a 24% and 49% decrease, respectively (Crosby et al., 2013). Furthermore, in bursting dopaminergic neurons, which signal salience, there is a pulse width–dependent increase in dopamine release, signifying more salience as more dopamine is released, with a maximal release at 1000 μs (Zweifel et al., 2009).

Number of Pulses

In burst firing, the probability of inducing a postsynaptic potential is determined by the amount of pulses within a burst (Snider et al., 1998). The effectiveness of signal transmission follows a non-linear curve and adding more pulses beyond five does not add much to effectiveness. That the number of pulses is not only important in burst firing but also in burst SCS is confirmed in an animal study (Crosby et al., 2015b). Whereas the number of pulses does not seem to determine the amount of cells that respond to burst SCS, it does influence neuronal activity, with more reduction obtained by a higher number of pulses (Crosby et al., 2015b).

Amplitude

The amplitude of the stimulation is important for the efficacy of burst SCS, as an animal study has demonstrated, both for reducing neuronal activity and for increasing the amount of responding neurons (Crosby et al., 2015b). In humans, no specific study has been performed to evaluate the importance of amplitude. However, the first clinical data suggest that low amplitudes suffice for obtaining pain suppression and that paresthesia, which is related to amplitude, is not required to obtain a beneficial effect (De Ridder et al., 2010a, 2013a). An intriguing question is whether this pain-suppressive effect could be nonlinear (i.e., follow an inverted-U curve), where low-intensity and high-intensity burst SCS could yield the same clinical effect. If so, an intermediate amplitude would be optimum. The reason for this question lies in the fact that activation of the dACC, which is modulated by burst but not tonic stimulation, follows an inverted-U shape (Viinikainen et al., 2010). Indeed, a clinical study suggests that there is group of patients who prefer high-amplitude stimulation and a group who prefer low-amplitude burst SCS to control their neuropathic pain (Tjepkema-Cloostermans et al., 2016).

Interspike Interval

The importance of the interspike interval has not been scientifically investigated, in either animal or human

studies. It is theoretically possible that the interspike interval has some influence on the nonlinear buildup of the postsynaptic potential, but data are lacking to support or refute this mechanism.

Total Charge

Whereas the initial pilot study on burst SCS suggested that burst stimulation was delivering more charge to the spinal cord (De Ridder et al., 2010a), it is questionable whether charge is of clinical importance in human burst SCS, even though an animal study with burst SCS does suggest so (Crosby et al., 2015b). Indeed, burst SCS is now routinely applied in cycle mode in a 1:2 to 1:3 ON:OFF protocol, which clinically suggests that the charge or energy delivery per second to the spinal cord might not be a determining factor for clinical efficacy but merely for generating APs.

IS BURST STIMULATION APPLICABLE TO THE ENTIRE NERVOUS SYSTEM?

Because burst firing is present in the entire nervous system, it intuitively makes sense to apply burst stimulation to the entire nervous system. And, indeed, clinical experience has shown that burst stimulation can be clinically successfully when applied to the peripheral nervous system (De Ridder et al., 2013b; De Ridder and Vanneste, 2015), to the spinal cord (Aitkin et al., 1978; De Ridder et al., 2010a, 2013a; de Vos et al., 2014; Kinfe et al., 2016; Schu et al., 2014; Van Havenbergh et al., 2015), to the somatosensory cortex (De Ridder et al., 2013c), to the auditory cortex (De Ridder et al., 2010b, 2011b), to the anterior cingulate cortex (De Ridder et al., 2016a,b), and to the dorsolateral, prefrontal cortex (De Ridder et al., 2012). The indications for burst stimulation were mainly tinnitus, pain, and alcohol addiction. Thus, a logical question that arises is whether burst stimulation would be applicable to other structures, and, if so, to which structures and for which clinical entities?

FUTURE TRENDS

Future trends for burst stimulation can be seen on two different levels: (1) new indications and new targets, and (2) modifications of the burst stimulation design.

New Indications and New Stimulation Targets

Both animal and human studies have demonstrated that burst firing is increased in many pathologies. Increased bursting is recorded in tinnitus (Jeanmonod et al., 1996; Norena and Eggermont, 2003), phantom pain (Jeanmonod et al., 1996; Lenz et al., 1998; Rinaldi et al., 1991), Parkinson disease (Jeanmonod et al., 1996; Wichmann and DeLong, 2003; Zirh et al., 1998), other movement disorders (Kanazawa et al., 1990), obsessive-compulsive disorder (Welter et al., 2011), epilepsy (Hodaie et al., 2006; Jeanmonod et al., 1996), addiction (Sun and Rebec, 2006) clinical depression (Jeanmonod et al., 1996), schizophrenia (Vukadinovic and Rosenzweig, 2012), and acute and chronic stress (Mana and Grace, 1997), suggesting that increased burst firing might be a common characteristic of certain human brain disorders (Jeanmonod et al., 1996). Because burst firing is related to calcium influx, via T channels, and the burst spikes are sodium channel based and the calcium outflux occurs via calcium pumps, different calcium and sodium channelopathies might be amenable to burst stimulation.

Based on these theoretical speculations, it does make sense to initiate trials of burst stimulation of the basal ganglia for Parkinson disease, dystonia, tremor, and other movement disorders. It also logically follows to apply burst stimulation to the DH for pain suppression and other indications, to trial burst stimulation at the anterior cingulate cortex for depression, and to stimulate the vagal nerve for epilepsy, depression, and other indications. Furthermore, burst SCS and C2 nerve field stimulation seem to defocus people from their symptoms (pain, tinnitus).

Modifications of the Burst Stimulation Design

Modifying the burst stimulation design will become essential to address specific issues that new targets and new indications bring to the table, adjusting the burst parameters to mimic the burst firing properties of those specific targets. However, some general improvements can be developed to prevent habituation to stimulation, to prevent seizure development for cortical implants, to potentially treat epilepsy, and to improve 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 addition could be both in time as well as in space or combined in space and time (De Ridder and Vanneste, 2016b). Pseudo-randomness in time means that the bursts in high frequency are presented in a pseudo-random way but at a specific frequency (De Ridder and Vanneste, 2016b). Basically, the interburst intervals vary in a random or pseudo-random way, but the amount of bursts and spikes do not change per second. In other words, both the burst and spike frequency remain the same. Also, the poles of the electrodes from which the current is delivered remain the same. In spatial, pseudo-random burst stimulation, the poles that are activated change in a pseudo-random way, but the burst firing itself remains rhythmic (De Ridder and Vanneste, 2016b). In combined temporal and spatial pseudo-random burst stimulation, the pseudo-randomness is a combination of both of

these pseudo-random burst stimulation designs. It creates a maximal variability, which would be foundational in preventing habituation to stimulation, as well as in preventing epilepsy in cortical stimulation and potentially treating epilepsy.

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. Basically, the stimulation design would mimic caressing the skin in an electronic form, thereby transmitting the pleasantness of tactile touch (Bjornsdotter et al., 2010; Loken et al., 2009), which is known to exert an antinociceptive effect (Liljencrantz and Olausson, 2014; Vrontou et al., 2013). This stimulation design could be called pleasure stimulation.

CONCLUSION

The development of burst stimulation was based on a very simple principle that mimicking naturally occurring firing patterns might be beneficial for neuromodulation. Its main benefit lies in the capacity of burst stimulation to modulate the salience (behavioral relevance) of any stimulus (Legrain et al., 2011; Mouraux et al., 2011), which is clinically expressed as (un)pleasantness or suffering and occurs physiologically via the medial pain pathway. Behaviorally, relevant stimuli focus the attention paid to the stimulus. Burst stimulation, in contrast to tonic stimulation, modulates not only the painfulness/loudness of a pain/sound stimulus and the descending inhibitory pain/sound system but also the suffering associated with it. Furthermore, it is capable of inducing pain suppression without the mandatory presence of paresthesia.

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