

Burst Spinal Cord Stimulation for Limb and Back Pain

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Key words

- Burst
- Dorsal column
- Neuromodulation
- Pain
- Paresthesia
- Spinal cord
- Stimulation

Abbreviations and Acronyms

EEG: Electroencephalography

PVAQ: Pain vigilance and awareness questionnaire

SCS: Spinal cord stimulation

VAS: Visual analog scale



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INTRODUCTION

Neuropathic pain results from lesions or diseases affecting the peripheral or central part of the somatosensory system and is notoriously difficult to treat. In 1967, Shealy et al. (33) implanted the first spinal cord stimulator as a treatment for neuropathic (cancer-related) pain. This was based on the gate-control theory proposed by Melzack and Wall (21), who postulated 2 years before the first implant that activity in large-diameter cutaneous fibers (type A β) inhibits the transmission of noxious information to the brain. It was conceptualized that electrical stimulation could activate large (A β) fibers, many of which are inactive at rest, and that this would produce a disproportionate relative increase of large fiber activity over small fiber activity (21). Mechanistically, the large fibers will suppress secondary neurons directly and

■ **OBJECTIVE:** Spinal cord stimulation via epidurally implanted electrodes is a common treatment for medically intractable neuropathic pain of different origins. Because tonic electrical stimulation evokes paresthesias over the painful area, this method has never been proven scientifically to be superior to placebo. Recently, burst stimulation (in which closely spaced, high-frequency stimuli are delivered to the spinal cord) has been developed, which does not generate paresthesias.

■ **METHODS:** A randomized placebo controlled trial in which we compared three stimulation paradigms (burst, tonic, and placebo) was performed on 15 consecutive pain patients. In contrast to tonic stimulation, burst stimulation was able to provide pain relief without the generation of paresthesias, permitting us to use a double-blinded placebo controlled approach. Primary outcome measures were visual analog scale pain scores for back pain, limb pain, and general pain. Secondary outcome measures included the pain vigilance and awareness questionnaire, which is used to measure attention to pain and pain changes, and visual analog scale of the worst, least, and momentary pain. In a subgroup of five patients, a source-localized electroencephalogram was performed under four conditions: baseline, tonic, burst, and placebo stimulation.

■ **RESULTS:** Burst stimulation was able to improve back, limb, and general pain by 51%, 53%, and 55% and tonic stimulation by 30%, 52%, and 31%, respectively. Pain now, least, and worst pain were improved by 50%, 73%, and 36% by burst stimulation, respectively, and 26%, 46%, and 13% by tonic stimulation. In comparison with placebo, burst, corrected for multiple comparisons, was significantly better for all measurements. However, the greatest differences were obtained in the pain vigilance and awareness questionnaire measurements: burst improved the attention to pain and pain changes, whereas tonic and placebo worsened these measurements. The analysis via encephalogram demonstrates burst stimulation activates the dorsal anterior cingulate and right dorsolateral prefrontal cortex more than tonic stimulation.

■ **CONCLUSIONS:** The differences between tonic and burst stimulation are likely attributable to a more-selective modulation of the medial pain pathways by burst stimulation, as shown by the activation of the dorsal anterior cingulate cortex.

indirectly via inhibitory interneurons, both of which are activated by pain-transmitting small (C and A δ) fibers (21).

In spinal cord stimulation (SCS), an extradural wire or paddle electrode is inserted overlying the dorsal columns of the spinal cord. After a successful externalized trial period, the stimulation lead is connected to an internal pulse generator, which delivers programmable electrical pulses to the spinal cord. This actually is an adaptation

from pacemaker technology (30) and has become a mainstream treatment for medically intractable neuropathic limb pain.

The pain-suppressing effect of SCS is likely related to a combination of a spinal and supraspinal mechanism (2, 31). The spinal mechanism involves antidromic activation of ascending dorsal column fibers, but SCS might also interact via orthodromic ascending fibers with descending serotonergic pain modulatory systems (37). SCS

is associated with enhanced gamma-aminobutyric acid (9) and acetylcholine (32) and reduced glutamate release in the dorsal horn (9).

All currently available pulse generators deliver tonic pulses that can be modified by altering the pulse width, frequency, and amplitude to produce maximal pain suppression. The internal-pulse generators can use either constant voltage or constant current to predominantly modulate the underlying A β fibers (22). Electrically stimulating A β fibers generates paresthesias (24), and therefore it is generally accepted that to obtain successful treatment of chronic, neuropathic pain by SCS, the stimulation-induced paresthesias have to cover the area of pain completely (23, 35), which prevents double-blind placebo controlled studies from being performed. This issue has been a recurring and persisting scientific criticism ever since its inception, even though more than 50,000 devices are implanted each year (36), fuelling a 1.5-billion dollar industry in 2010. One of the reasons for this success is that SCS has been shown to be cost effective for failed back surgery syndrome over conventional medical treatment (1, 3) and reoperation (20) associated with better pain suppression (1, 3, 20).

Recently a novel stimulation paradigm was developed called burst stimulation (10). This was conceived, in a Gaudi-like fashion, on the basis of the dual firing

properties of thalamic cells, which can fire in tonic and burst modes (14). Because thalamic burst firing was considered a more powerful activator of the cortex than tonic firing (39), a kind of wake-up call from the thalamus (34), it was first applied successfully on the auditory cortex (11) and later translated to the spinal cord (10). Burst stimulation consists of intermittent packets of closely spaced, high-frequency stimuli, for instance, 40-Hz burst mode with five spikes at 500 Hz per burst, with a pulse width of 1 ms and 1-ms interspike intervals delivered in constant current mode. The cumulative charge of the five 1-ms spikes is balanced during 5 ms after the spikes (10), which differentiates it from high-frequency clustered firing, in which each pulse is immediately charge balanced (Figure 1). This finding has permitted us, for the first time in 45 years, to scientifically prove that SCS is better than placebo stimulation. Our study was therefore initiated to find out whether SCS is indeed capable of suppressing neuropathic limb pain in a placebo-controlled way.

METHOD AND MATERIALS

Participants

Fifteen patients, 4 men and 11 women were included in this study. Patients' ages ranged between 39 and 68 years, with a mean of 54.07 years. These 15 consecutive patients

who presented to the BRAI²N neuro-modulation clinic were eligible for SCS according to the Belgian requirements for the reimbursement for SCS, which states that the patient has to be medically intractable to opioids and antiepileptic drugs. All patients were selected by the first author, and after a multidisciplinary discussion with a specialized pain physician, a psychological and psychiatric evaluation was performed to rule out psychogenic pain as well as other psychiatric morbidity contraindicating an implant. After authorization by the psychologist and psychiatrist, an implant was offered to the patient. All 15 patients were included in the study, which was conducted from January 1, 2011, until September 30, 2011, and was approved by the Antwerp University Hospital Institutional review board ('Comité voor medische ethiek') and registered at ClinicalTrials.gov (NCT01486108).

Implantation

All patients underwent the implantation of a lamitrode (St. Jude Medical, Neurodivision, Plano, Texas, USA) via laminectomy under general anesthesia (see patient overview in Table 1). During the mandatory period of external stimulation, which is a minimum of 28 days according to Belgian health care requirements for reimbursement, each patient was trialed by application of the classical tonic stimulation (40 or 50 Hz), burst stimulation with the same electrode

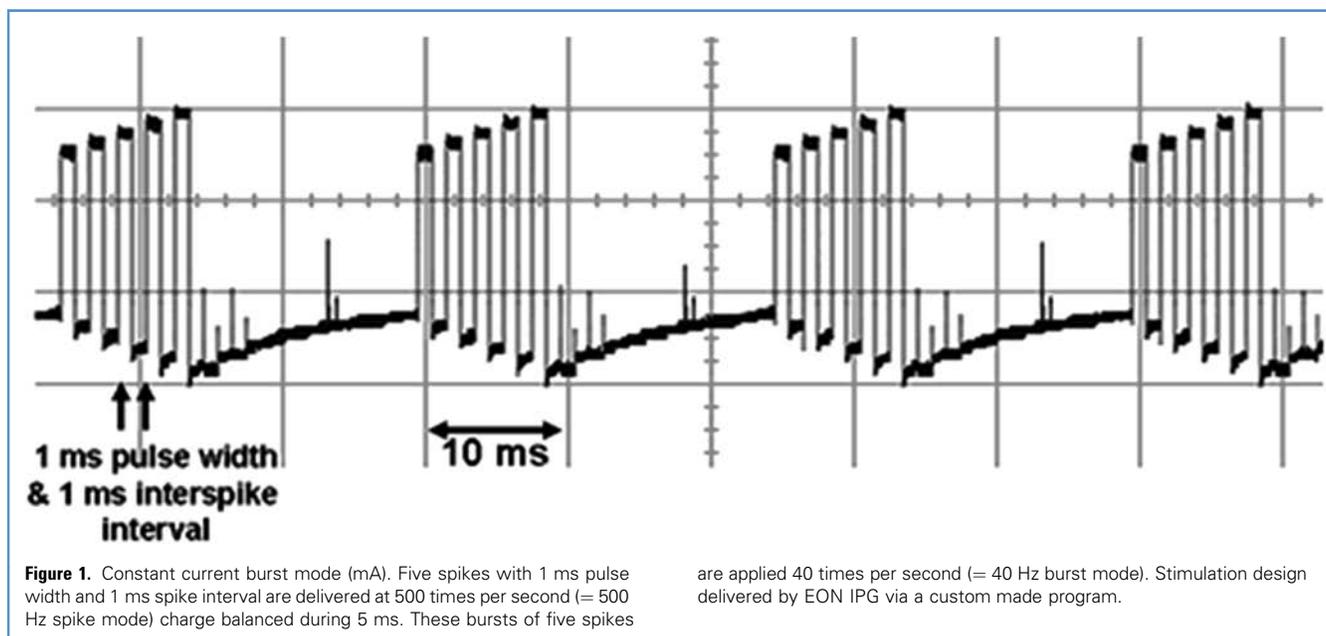


Table 1. Overview of Patient Age, Gender, Indication, Surgeries, Electrode Used, and Electrode Position

Patient	Age	Gender	Indication	Surgeries	Electrode Used	Electrode Position	Back Pain*	Limb Pain*	General Pain*
1	46	M	FBSS	5	Lamitrode tripole	Thoracic	7.2	6.8	7.3
2	68	F	FBSS	2	Lamitrode 88	Thoracic	9.5	8	9.4
3	43	F	FBSS	1	Lamitrode tripole	Thoracic	7.4	3.7	4.9
4	53	F	FBSS	3	Lamitrode penta	Thoracic	5.8	7	7
5	55	M	FBSS	2	Lamitrode 88	Thoracic	8.6	8.3	8.5
6	52	M	FBSS	5	Lamitrode penta	Thoracic	8.9	9.3	9.2
7	57	F	FBSS	4	Lamitrode penta	Thoracic	8.8	6.5	8.9
8	51	M	FBSS	5	Lamitrode tripole	Thoracic	8.6	8.8	8.9
9	48	F	Myelopathy	—	Lamitrode 44	Thoracic	4.9	7.6	7.6
10	62	F	FBSS	2	Lamitrode 88	Thoracic	6.9	7.5	7.6
11	39	F	FBSS	1	Lamitrode 88	Thoracic	1.6	9.2	9.1
12	51	F	FBSS	2	Lamitrode 88	Thoracic	8.8	6.4	8.6
13	67	F	FNSS	1	Lamitrode 44	Cervical	10	5.4	8.4
14	54	F	Myelomalacia	1	Lamitrode 88	Thoracic	3.3	8	8
15	65	F	FBSS	2	Lamitrode 88	Thoracic	10	10	10

M, male; FBSS, failed back surgery syndrome; F, female; FNSS, failed neck surgery syndrome.

*Visual analog scale pain scores (10 being the highest degree of pain).

configuration on separate days to prevent a carryover effect, and placebo.

Patients were told they would receive three stimulation designs, some of which they might feel as paresthesias and some of which they might not feel as paresthesias. After an initial tonic programming session to define which electrodes needed activation as determined by paresthesia coverage, patients were programmed, lying down, randomly for 1 week with burst mode, 1 week in tonic mode, and 1 week with placebo. The patients were discharged home on the second postoperative day and were instructed not to change the stimulation parameters during the next week. They were only allowed to use a magnet for forcefully stopping stimulation in case of emergency.

At the end of each week, the patients returned to the outpatient clinics, where they presented a report consisting of the visual analog scale (VAS) and pain vigilance and awareness questionnaire (PVAQ) scale (see below) to the blinded evaluator, after which they were reprogrammed for the next stimulation week by the programmer. Reprogramming consisted of first turning off the stimulator and when the patient mentioned the pain had recurred to its prestimulation levels, the new stimulation set was applied.

Because the Belgian reimbursement system mandates a minimum of 28 days of externalized stimulation, the 3 weeks of randomized stimulation was performed with a nonsterile EON IPG System (St. Jude Medical) via externalized extension wires. The limb pain area was covered in all patients with paresthesias, and the paresthesias were not perceived by the patients as uncomfortable. The stimulation intensity for tonic and burst mode during randomized stimulation was selected on the basis of the maximal pain suppression as determined by the patient.

The burst mode was programmed by use of a custom-made software and programming device. Typically, burst stimulation is characterized by a lower amplitude but larger pulse width, which results in a similar energy delivery per pulse (10). In burst mode, the amplitude was increased up to the moment that paresthesias were elicited. Subsequently, the amplitude was decreased to a level below paresthesia threshold.

The cumulative charge of the five 1-ms spikes is balanced during 5 ms after the spikes, and charge balancing is not complete after each individual spike. This differentiates burst mode from intermittent high frequency stimulation. Placebo stimulation

was performed in the following way: burst stimulation was applied on the predefined electrode contacts until the patient experienced paresthesia. Subsequently the stimulator intensity is decreased exactly like in burst programming but continued until zero amplitude.

Measurements

Primary outcome measures were the pain VAS, which consists of a 100-mm line for limb pain, back, and general pain. General pain is defined as a global pain score experienced during the past week. Secondary outcome measures were VAS scores for pain now, worst pain, and least pain during the last week, as well as the PVAQ scale. The PVAQ measures the preoccupation with or attention to pain and is associated with pain-related fear and a person's perceived severity of pain (29). It consists of two separate factors that measure (1) attention to pain and (2) attention to changes in pain (29). Paresthesias caused by the stimulation were scored on a VAS consisting of a 100-mm line at stimulation amplitudes that are needed to suppress pain to verify whether the double-blind, placebo-controlled study was performable (Supplementary Table 1).

Electroencephalography (EEG) Data Collection and Source Localization

EEG recordings (Mitsar-201; NovaTech: <http://www.novatecheeg.com/>) were obtained in a quiet and dimly lighted room with each participant sitting upright on a small-but-comfortable chair. The EEGs were performed at baseline and at the end of each week of burst, tonic, and placebo stimulation in five of the investigated patients. Average Fourier cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–44 Hz). Standardized low-resolution brain electromagnetic tomography was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the eight frequency bands (Supplementary Table 1) (25).

Statistics

Statistics for the behavior measurements as well as for the source localization can be found in the Supplementary Table 1.

RESULTS

The mean pain score on VAS preoperatively for axial pain was 7.4, for limb pain was 7.5, and pain in general was 8.2. For the PVAQ, the baseline score for attention to pain was 15.9 and for attention to changes in pain 18.6. For VAS scores for pain now, least pain, and worst pain the baseline scores were 7.3, 5.3, and 7.9, respectively. After 4 weeks, patients were asked which stimulation design they preferred: all patients preferred burst mode. No patient indicated that tonic stimulation was unbearable.

A comparison between placebo, tonic, and burst stimulation indicated that tonic stimulation created significantly more paresthesias in comparison with placebo and burst stimulation ($F = 5.04$, $P < 0.05$; Figure 2). No significant difference was found between placebo and burst stimulation, demonstrating that burst stimulation did not induce more paresthesias than placebo, which permitted us to evaluate the data further.

A comparison between placebo, tonic, and burst stimulation over the three primary outcome measures (back pain, limb pain, and general pain) revealed an overall significant effect ($F = 4.31$, $P < 0.05$). Univariate tests of the three primary outcome measures

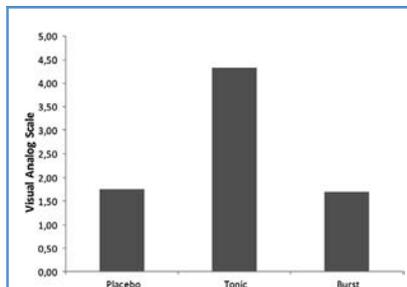


Figure 2. A comparison of placebo, tonic, and burst stimulation for the question “How much paresthesia do you feel as a consequence of stimulation?” Responses revealed a significant effect ($F = 5.04$, $P < 0.05$). A pairwise comparison adjusted for multiple comparisons (Bonferroni) demonstrated that tonic stimulation induces significantly more paresthesia in comparison with placebo and burst stimulation ($P < 0.05$). No significant difference was found between placebo and burst stimulation for paresthesia.

separately revealed that burst stimulation significantly differs from placebo stimulation for back pain, limb pain, and general pain, respectively (Table 2 and Figure 3). Post hoc analysis revealed that the burst stimulation resulted in significantly more improvement than placebo stimulation. No significant difference was obtained between tonic and burst stimulation for back pain and limb pain, respectively. However, a significant difference was obtained between tonic and burst stimulation for general pain, demonstrating that during burst stimulation a better suppression was obtained than during tonic stimulation. No significant

effect was found for order after we including it in the analysis, thus disproving that the obtained results were related to a carryover effect of the previous stimulation.

For back pain, no significant effect was obtained between tonic and placebo stimulation. However, analysis yielded a significant effect between tonic and placebo for limb pain and general pain, indicating that tonic stimulation had better pain suppression than placebo stimulation. In an additional analysis, we included the order stimulation parameters for each subject as a covariant. No significant effect was obtained for order. However, the effect of burst remained.

For the secondary outcome measures, it was shown that both tonic and placebo stimulation had no effect on the “attention to the pain” and the “attention to the changes in pain,” as measured with the PVAQ, in contrast to burst stimulation. Only burst stimulation was able to improve the amount of attention the patients paid to pain and changes in pain in a statistically significant way. For an overview of our findings, see Table 3. No effect was found for order of stimulation after we included it in the analysis.

In addition, a comparison between the different VAS scales for pain (now, least, and worst) indicated that burst significantly differs from placebo stimulation. That is, during burst stimulation patients had less pain at the present moment, had lower pain if they checked for the worst pain during the last 7 days, as well as for pain if they checked

Table 2. Primary Outcome Measure: Mean Improvement (VAS Baseline Minus VAS Stimulation; Placebo, Tonic, and Burst) for Back Pain, Limb Pain, and General Pain

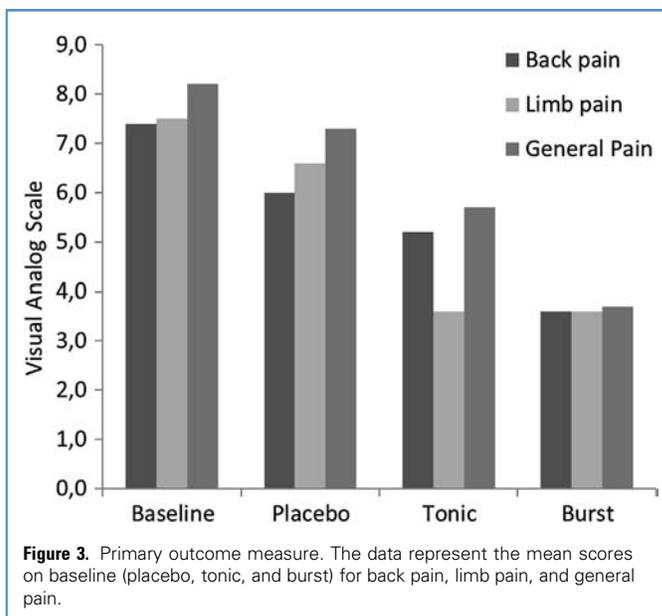
	Placebo		Tonic		Burst		F Value
	RD	%	RD	%	RD	%	
Back pain	1.4a	18.9	2.2a,b	30.3	3.8b	51.3	6.20*
Limb pain	0.9a	11.7	3.9b	51.5	3.9b	52.7	4.66†
General pain	0.9a	10.9	2.5b	30.9	4.5c	55.0	7.44*

VAS, visual analog scale.

Both the raw improvement (RD) as well as the percentage change (%) is reported. A comparison between placebo, tonic, and burst stimulation over the three primary outcome measures (back pain, limb pain, and general pain) revealed an overall significant effect ($F = 4.31$, $P < 0.05$).

Superscripts indicate significant differences between the different stimulation parameters. Numbers with a different superscript differ significantly from each other after correction for multiple comparisons (Bonferroni).

* $P < 0.01$, † $P < 0.05$; thus, in contrast to tonic stimulation, burst stimulation is significantly better than tonic stimulation for back pain relief but not for limb pain improvement. Both tonic and burst pain are significantly better than placebo for general pain improvement, and burst is significantly better than tonic stimulation for general pain.



for the least pain during the last 7 days. For tonic stimulation in comparison with placebo, a significant effect was obtained for pain now and least pain, respectively, but not for worst pain. When we compared tonic versus burst stimulation, a significant effect was obtained for both least pain and worst pain, indicating that burst has better results. No significant difference was found between tonic and burst stimulation for pain at the moment. For an overview, see **Table 3**. No effect was found for order of stimulation after we included it in the analysis.

Furthermore, source localization on the EEG recordings revealed a significant increase in synchronized activity in the left and right dorsal anterior cingulate cortex for the alpha1 frequency band and the left dorsal lateral prefrontal cortex for the alpha1, beta2, and beta3 frequency bands for burst stimulation in comparison with tonic stimulation (**Figure 4** and **Supplementary Table 1**). Comparing burst with both the baseline and the placebo revealed an increase of alpha activity of dorsal anterior cingulate cortex and decrease of gamma activity of parahippocampus after burst stimulation (**Supplementary Table 1**). After tonic stimulation, a comparison between tonic stimulation and placebo indicated a significant decrease in beta3 activity in the posterior cingulate cortex and decrease of gamma activity in the posterior insula (**Supplementary Table 1**).

DISCUSSION

A first critically important finding of this study was that burst SCS did not generate more paresthesias than placebo stimulation, which permitted us to further analyze our results using a double-blinded placebo

controlled study. This result is in contrast to tonic stimulation, which did generate significantly more paresthesias than placebo and burst stimulation.

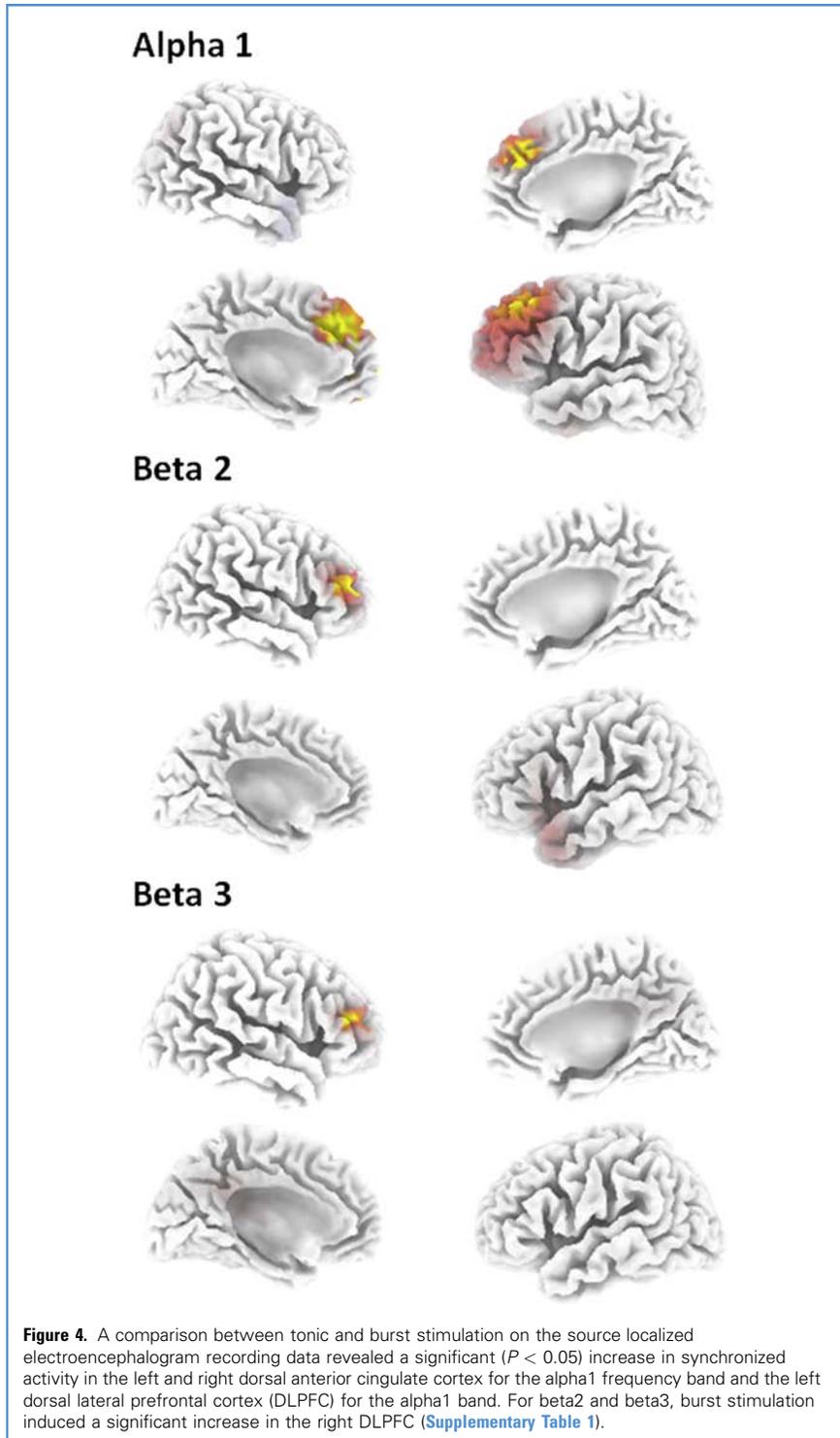
Thus, for the first time we demonstrated, in a double-blinded placebo controlled way, that (burst) SCS is indeed capable of suppressing pain in a statistically significant and clinically relevant way for limb pain, back pain, and pain in general and for the patient’s current pain, least pain, and worst pain.

Tonic stimulation, on the other hand, did not seem to be superior to placebo stimulation for pain suppression when pain was at its worst, nor did it seem to suppress back pain significantly. And indeed, SCS has predominantly been used for treating intractable, chronic neuropathic pain component in the extremities; however, several investigators have reported an improvement in patients’ back pain (17, 33, 40) even though axial low back pain has been shown to be more difficult to suppress. Because there was no significant difference between the improvement noted in back pain in comparison with placebo stimulation for tonic stimulation, it is possible that suppression of back pain could be the result of a placebo effect. In this study, however, burst

Table 3. Secondary Outcome Measures: Baseline Minus the Stimulation Parameter (Placebo, Tonic, and Burst) for PVAQ (Attention to Pain and Attention to Changes in Pain) and the VAS Scales (Pain Now, Least Pain During the Last 7 Days, and Worst Pain During the Last 7 Days)

	Placebo		Tonic		Burst		F Value
	RD	%	RD	%	RD	%	
PVAQ							
Attention to pain	0.5 ^a	3.3	0.8 ^a	5.0	1.2 ^b	7.6	6.57*
Attention to changes in pain	0.6 ^a	3.2	0.7 ^a	3.9	1.9 ^b	10.0	4.93*
VAS scales							
Pain now	0.9 ^a	12.8	1.9 ^b	26.0	3.6 ^b	49.8	6.36*
Least pain (last 7 days)	1.1 ^a	21.7	2.4 ^b	45.8	3.8 ^c	73.2	6.02*
Worst pain (last 7 days)	0.05 ^a	0.6	1 ^a	12.6	2.8 ^b	36.0	4.63*

PVAQ, pain vigilance and awareness questionnaire; VAS, visual analog scale. Both the raw difference (RD) as well as the percentage change (%) is reported. Superscript indicates statistically significant differences between the different stimulation parameters. Numbers with a different superscript differ significantly from each other after correction for multiple comparisons (Bonferroni). For pain now and least pain, tonic stimulation is better than placebo but not for worst pain. Burst stimulation is better than tonic stimulation for least pain and worst pain improvement. *P < 0.05; no statistically different changes are noted between the two subscales of the PVAQ for tonic versus placebo, but burst differs significantly from placebo and tonic stimulation for both measures of PVAQ.



stimulation also suppressed patients' back pain in a statistically significant and clinically relevant way, in an order of magnitude not much different from the extremity pain component.

Burst stimulation in contrast to tonic stimulation seemed to have a dramatically different effect on the attention paid to pain and pain changes, analogous to cingulotomy (6, 7, 12). A functional magnetic resonance

imaging study performed during SCS has demonstrated that tonic stimulation modulates predominantly the lateral pain system, as blood oxygenation level–dependent changes were noted in the primary sensorimotor area, posterior insula, and secondary somatosensory cortex (38). Because attention to pain is mediated via the anterior cingulate cortex (6, 15), which is part of the medial pain system, it can be hypothesized that burst stimulation not only modulates the lateral discriminatory pain system but also the medial affective/attentional pain system. Thus, burst stimulation could exert a clinical effect analogous to what pain patients experienced in frontal lobotomies. In the words of Walter Freeman: “Prefrontal lobotomy changes the attitude of the individual towards his pain, but does not alter the perception of pain. Whereas, previous to the operation it occupied the focus of his attention, after lobotomy pain fades into the background” (12).

The PVAQ changes indeed demonstrate this, as do the burst stimulation–induced changes in worst and least pain scores. Only burst stimulation is better than placebo in altering the subject's attention to pain and pain changes, and burst is significantly better than tonic stimulation for addressing the worst and least pain. Rather than being a more powerful pain suppressor, burst stimulation might therefore exert its main effect by an attention-modulating effect, as evidenced by both the clinical differences between burst and tonic stimulation and the neurophysiological differences at the level of the anterior cingulate.

Pain stimuli are indeed processed in parallel (13) by two pathways: a medial affective/attentional pain pathway and a lateral discriminatory pathway (15, 27, 28). The medial system is triggered by nociceptive-specific neurons, firing in burst mode, and relayed in lamina I of the spinal horn to the mediodorsal and ventromedial nucleus of the thalamus and from there to the anterior cingulate cortex, anterior insula, and amygdala. The lateral system is triggered predominantly by the wide dynamic range neurons, firing in tonic mode and relaying in lamina I and IV–VI of the dorsal horn to the VPL and VPM nucleus of the thalamus and from there to the primary and secondary somatosensory cortex, posterior parietal area (8, 19, 27).

The source-localized EEG data obtained in a subgroup of five patients indeed

supports this proposed mechanism, as burst stimulation is characterized by significantly more alpha activity in the dorsal anterior cingulate, a component of the medial pain pathway, in comparison with tonic, placebo, and baseline. The dorsolateral prefrontal activation both for alpha and beta oscillatory activity during burst stimulation is also related to the affective and attentional processing of the pain stimuli (26), as transcranial direct current stimulation of the dorsolateral prefrontal cortex can both change the emotional and the perceptual pain components (4, 5).

The reason why burst stimulation does not generate more paresthesias than placebo is unknown, but a hypothesis has been forwarded (10). One potential explanation is that the charge per pulse does not differ significantly between burst and tonic stimulation, even though the amplitude is significantly lower, most likely because of the larger pulse width of the burst design and the lower amplitudes delivered with burst stimulation (10) could induce sub-threshold stimulation of the A β fibers, which have been implicated in the generation of paresthesia (24). Burst stimulation could therefore already suppress pain via the electrophysiological gate control mechanism before the clinical paresthesia threshold is reached. This hypothesis should be verified by further neuroscientific research.

The results of this study were obtained after a short-term evaluation. However, the first, albeit-uncontrolled, study has shown that the results remain very stable in patients for at least 2 years, permitting us to draw firm conclusions that are very likely stable and robust.

Gender does not seem to significantly influence outcome in SCS (16, 18). However, in view of the skewed gender demographic in this study population (4 men, 11 women) it cannot be excluded that gender influences the results of burst stimulation. In summary, this study demonstrated that burst SCS was capable of suppressing neuropathic pain better than placebo in a statistically significant and clinically relevant way, possibly because burst stimulation modulates the medial pain system.

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Focus On the Cover: Istanbul, the Bosphorus (Bogaziçi) (right), Golden Horn (Haliç) (branching left), Sultan Ahmed Mosque (Sultanahmet Camii) and Hagia Sophia (Ayasofya) (both lower left), and the Bosphorus Bridge (Bogaziçi Köprüsü) connecting Europe and Asia, are shown at sunrise.

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Supplementary Table 1. Significant Results ($P < 0.05$) for Source-Localized EEG Recordings Comparing Baseline, Tonic Burst, and Placebo Stimulation

	MNI Coordinates			Maximum Voxel Value	Brodmann Area	Name
	X	Y	Z			
Baseline vs. tonic						
Beta 3	0	-45	35	-2.93	31	R PCC
	-5	-45	35	-2.92	31	L PCC
	5	-50	35	-2.90	23	R PCC
Gamma	-25	-50	-5	-3.70	19	L PHC
	-25	-55	0	-3.68	30	L PHC
Baseline vs. burst						
Alpha 1	5	35	30	4.14	32	R dACC
	-10	35	25	4.02	32	L dACC
	-5	40	35	4.45	9	L DLPFC
Gamma	10	-45	0	3.31	30	R PHC
	15	-45	-5	3.27	19	R PHC
Baseline vs. placebo						
n.s						
Placebo vs. tonic						
Beta 3	-5	-45	40	-3.52	31	L PCC
Gamma	-31	-40	20	-3.63	13	L pl
Placebo vs. burst						
Alpha 1	-15	35	24	3.50	32	L dACC
	-33	39	38	3.13	9	L DLPFC
Gamma	-9	-45	2	-2.58	30	L PHC
	12	-45	2	-3.20	30	R PHC
Tonic vs. burst						
Alpha1	-6	25	29	3.65	24	L dACC
	-10	25	34	3.27	32	L dACC
	-35	29	42	3.14	9	L DLPFC
	10	25	29	3.14	32	R dACC
	8	25	19	3.00	24	R dACC
Beta2	44	42	17	3.64	46	R DLPFC
Beta3	44	26	38	3.66	9	R DLPFC

EEG, electroencephalogram; MNI, Montreal Neurological Institute; R, right; PCC, posterior cingulate cortex; L, left; PHC, parahippocampus; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; n.s., not significant; pl, posterior insula.

Maximum voxel value for each significant Brodmann area as well as the exact MNI coordinate are shown for each comparison.

Alpha1 (8–10 Hz), Beta2 (18.5–21 Hz), Beta3 (21.5–30 Hz), and Gamma (30.5–45 Hz).