Received: December 18, 2018 Revised: March 9, 2019 Accepted: March 19, 2019

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12960

Comparison of Neural Activity in Chronic Pain Patients During Tonic and Burst Spinal Cord Stimulation Using Fluorodeoxyglucose Positron Emission Tomography

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Objective: Burst spinal cord stimulation (SCS) is a novel stimulation paradigm that seems to provide better pain relief compared to the classic tonic SCS with minimal paresthesia sensation. Based on source localized electroencephalography and clinical data, it has been proposed that burst stimulation as defined by Dirk De Ridder exerts this greater effect by not only modulating the lateral and the descending pain-inhibitory pathways (similar to tonic SCS) but also modulating the medial pain pathway, which encodes the affective, motivational aspects of pain.

Material and Methods: The current study evaluates the supraspinal differences between burst and tonic stimulation with another functional imaging technique, namely fluorodeoxyglucose positron emission tomography (FGD-PET) scanning, in seven patients, who underwent both burst and tonic SCS, to confirm this notion of medial pain pathway modulation.

Results: The results of the current FGD-PET study show that burst stimulation, in contrast to tonic stimulation, indeed modulates the dorsal anterior cingulate cortex (i.e., medial pain pathway) more than tonic stimulation.

Discussion: Our data suggest an inherent difference in the central neural mechanisms during burst and tonic stimulation, which could potentially alter the patient's perception of pain.

Keywords: Anterior consulate, burst, dorsal anterior cingulate cortex, lateral pathway, medial pathway, pain, PET scan, spinal cord stimulation

Conflict of Interest: Dr. Yearwood, Dr. De Ridder, Dr. Falowski, and Dr. Vanneste are the consultants of Abbott. Dr. Venkatesan is an employee of Abbott. Hye Bin Yoo and Dr. Wing Ting To have no conflicts of interest to report.

INTRODUCTION

Spinal cord stimulation (SCS) is a removable, safe, and cost-effective treatment that has been approved by the FDA for the treatment of chronic pain of the trunk and limbs, intractable lower back and leg pain, pain from failed back surgery syndrome, *complex regional pain syndrome,* refractory angina, and critical limb ischemia (1–3). Research has demonstrated that tonic SCS has the ability to reduce pain, reduce analgesic consumption, improve quality of life, and allow some patients to return to work with minimal side effects besides paresthesia (4). In SCS, an electrical lead with a thin wire is placed through a needle in the back near the spinal cord. This is connected to a programmable generator that emits electrical currents to the spinal cord (5). Traditional SCS produces tonic waveforms consisting of continuous individual pulses delivered at the same frequency (or interpulse interval), duration (pulse width), and amplitude (6,7) (Fig. 1). The underlying mechanism of action is based on Melzack and Wall`s gate control theory, which suggests that C-fibers that transmit the chronic sensation of pain to the brain can be reduced directly and indirectly by inhibitory interneurons that receive signals from Aβ-fibers and can subsequently block transmission of pain information to the brain (8). The assumption is that electrical stimulation to the spinal cord mainly stimulates these Aβ-fibers and leads to "closure of the gate" by C-fibers, which reduce the pain percept. Meanwhile, electrical stimulation elicits a tingling sensation (i.e., paresthesia) in the corresponding dermatomes.

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: This work was supported by Abbott through a sponsored clinical research study.

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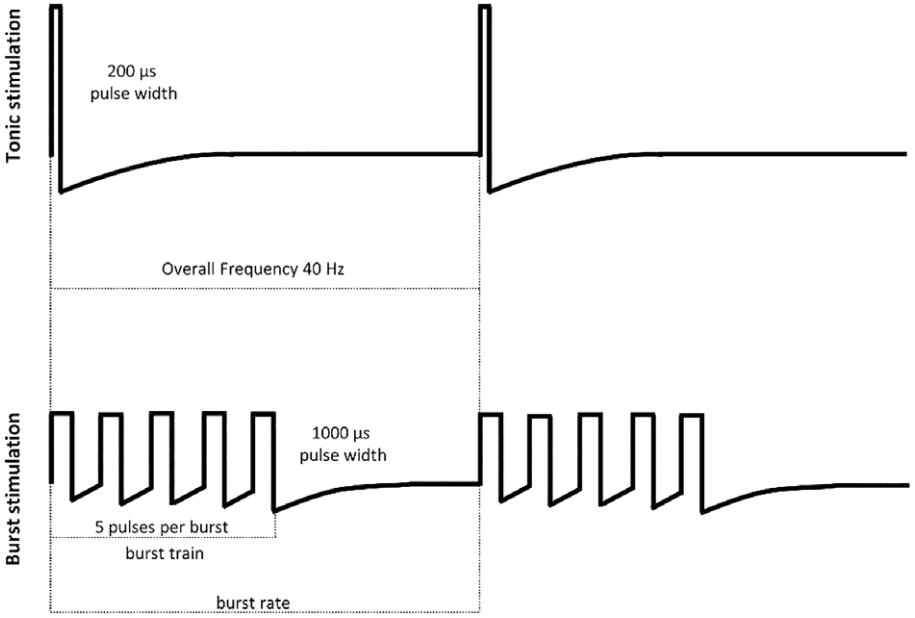

Figure 1. Schematic overview of tonic and burst stimulation.

Burst SCS as developed by Dirk De Ridder is a novel stimulation paradigm that delivers groups of pulses at a higher frequency (charge) and at amplitudes much lower than tonic stimulation (9,10) (Fig. 1). This charge phase is separated by pulse-free interphase delays, ultimately followed by a passive recharge (discharge) phase, allowing recovery (9,10). It has been suggested to provide better pain relief to tonic SCS (9,11–13) with fewer reported sensations of paresthesia (9,10,13), which is typically observed with conventional tonic stimulation. Burst stimulation has further been found to mimic naturally occurring burst firing patterns involved in pain processing (14,15).

A comparison of the central neural activation patterns during tonic and burst stimulation has the potential to investigate the differences in neural processing and the underlying mechanisms involved in modulating the perception of pain. Pain is believed to be processed by at least three pathways, namely the lateral and medial pain-evoking pathways and a descending pain-inhibitory pathway (16). The lateral and medial pathways process pain information in parallel and are, respectively, involved in the pain processing via C, Aδ, and Aβ-fibers through the ventralposterolateral nuclei of the thalamus to the somatosensory cortex (17). The C-fibers are connected to the mediodorsal nuclei of the thalamus that send information to the insula and anterior cingulate cortex (18). While the lateral pathway is involved in the pain percept itself, the medial pathway encodes the affective component of pain (18,19). The descending pain inhibitory pathway involves the rostral and pregenual anterior cingulate cortex. This region connects to the periaqueductal gray, which in turn relays information to the somatosensory periphery (17). Recent research has suggested that burst and tonic SCS modulate both the ascending lateral pathway and descending pain inhibitory pathway (16). It was further demonstrated that burst stimulation exerts a different effect on attention to pain and pain changes compared to tonic stimulation by its ability to also modulate the medial pain pathway (9,10,16). These changes in the medial pain pathway, along with the changes in the descending pain inhibitory pathway, could explain the positive results described by burst SCS in comparison to tonic stimulation (9,10,12–14,20–23).

While initial research has been done with source localized electroencephalography (EEG) (16), in this study, we look for confirmation or refutation by other functional imaging techniques is essential. As there was no fMRI compatible SCS burst system, in this study, we aim to elucidate the differences in neural activity evoked during tonic and burst stimulation and assess corresponding correlation with patient reported pain scores using fluorodeoxyglucose positron emission tomography (FGD-PET), which uses an analog of glucose as the biologically active tracer molecule.

METHODS

Design

This study was a sub-study of the prospective, multicenter, randomized, open label, crossover study SUNBURST study. The SUNBURST trial had been approved by the local Institutional review board, registered on Clinical Trials (NCT02011893) and this sub-study, adding the FGD-PET and the Pain Vigilance and Awareness Questionnaire (PVAQ) in one study site, had been approved as an addition to the original protocol. The SUNBURST study is under an Investigational Device Exemption (IDE), protocol C-12-07 ver. 8.28.14 (7). All seven patients are from one site of the SUNBURST study, under the medical supervision of Dr. Thomas Yearwood from the Comprehensive Pain & Rehabilitation, were assessed with additional FGD-PET and the pain vigilance and awareness questionnaire (PVAQ) for this sub-study. Patients were collected as an extra visit within the SUNBURST study. They were randomized 1:1 to receive either tonic or burst stimulation delivered using a SJM Prodigy™ system. Table 1 shows the inclusion and exclusion criteria. Patients were programmed according to the group assignment designated in the randomization envelopes. Subjects were randomly assigned to tonic stimulation or burst stimulation. Subjects and investigators were blinded to the treatment groups. Programming was performed by qualified personnel in accordance to the site standards of clinical care. Subjects received either tonic or burst stimulation for 12 weeks. At the end of the 12 weeks, patients crossed over from burst to tonic stimulation or vice versa. A PET scan was taking at baseline and after 12 weeks of tonic stimulation and after 12 weeks of burst stimulation. It is however important to note that tonic stimulation

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Table 1. Inclusion and Exclusion Criteria.

Inclusion criteria:
- Subject is 22 years of age or older.
- Subject has chronic intractable pain of the trunk and/or limbs.
- Subject has an average score of 60 or higher for average daily overall pain on the visual analogue scale (VAS) 7 day pain diary.
- Subject has attempted "best" medical therapy and has tried and failed at least three documented medically supervised treatments (including, but not limited to physical therapy, acupuncture, etc.) and has failed medication treatment from at least two different classes.
- Subject's pain-related medication regimen is stable 4 weeks prior to the baseline evaluation.
- Subject agrees not to add or increase pain-related medication from activation through the 24 week follow-up visit.

Exclusion criteria:
- Subject is currently participating in a clinical investigation that includes an active treatment arm.
- Subject has been implanted with a previous neurostimulation system or participated in a trial period for a neurostimulation system.
- Subject's overall Beck Depression Inventory II Score is >24 or has a score of 3 on question 9 relating to suicidal thoughts or wishes at the screening visit.
- Subject has an infusion pump or any implantable neurostimulator device.
- Subjects with concurrent clinically significant or disabling chronic pain problem that requires additional treatment.
- Subject has an existing medical condition that is likely to require repetitive magnetic resonance imaging (MRI) evaluation in the future (i.e., epilepsy, stroke, multiple sclerosis, acoustic neuroma, and tumor).
- Subject has an existing medical condition that is likely to require the use of diathermy in the future.
- Subject's pain originates from peripheral vascular disease.
- Subject is immunocompromised.
- Subject has documented history of allergic response to titanium or silicone.
- Subject has a documented history of substance abuse (narcotics, alcohol, etc.) or substance dependency in the 6 months prior to baseline data collection.
- Female candidates of child bearing potential that are pregnant (confirmed by positive urine/blood pregnancy test).

generates paresthesia due to activation of the Aβ-fibers, while burst stimulation induces no or almost no paresthesia (9,10). This makes blinding more challenging. It is however important to note that the patients were naïve to both tonic and burst stimulation and did not know what stimulation is associated with paresthesia.

Implantation and Programming

The SCS trial evaluation period, per usual care (approximately 3 to 10 days), was performed with epidural leads placed percutaneously under local anesthesia and connected to an external pulse generator that delivers tonic stimulation (Abbott, Plano, TX). The implanted SCS device, Prodigy™ (Abbott), a constant current generator, is capable of delivering both tonic and burst waveforms. Surgical implant of the permanent system occurred approximately 4 to 8 weeks after the end of the trial evaluation period, pursuant to usual care and surgical scheduling. After the permanent implant, a surgical recovery period of 2–3 weeks was planned to allow for wound healing during which transient medication increases were allowed. Tonic stimulation pulse width was programmed in the usual range of 100–500 μs, and tonic stimulation frequencies were set at between 30 and 100 Hz. Amplitudes for tonic stimulation were programmed according to individual participant perception to a level that typically produces comfortable paresthesia. Burst programming for this study followed specific parameters such that 500-Hz stimulation was delivered in groups of five pulses with 1-ms pulse width, with bursts repeated 40 times per second. Charge balance occurred during the 5 ms after each burst with passive repolarization. Amplitudes for burst stimulation were programmed according to individual participant perception. During the control phase of the study, participants were advised that they might or might not experience paresthesia at the outset of both waveforms.

Behavioral Measures

The outcome parameters for the efficacy of treatment were assessed with a visual analogue scale (VAS) for pain and the pain vigilance and awareness questionnaire (PVAQ). These measures assessed the overall impact of pain intensity and the emotional component related to pain. The measures were conducted at baseline, prior to implantation, and at the end (after 12 weeks) of each of the two study arms ("tonic stimulation" or "burst stimulation").

The VAS pain consists of a straight line of 10 cm with the endpoints defining extreme limits such as "no pain at all" and "pain as bad as it could be." The patient is asked to mark his widespread muscle pain level on the line between the two endpoints. The distance between "no pain at all" and the mark then defines the subject's pain.

The PVAQ measures preoccupation with or attention to pain and is associated with pain-related fear and perceived pain severity. It consists of 16 items measured on a 6-point scale (24).

PET Data Collection and Processing

The patients were instructed to avoid caffeine and alcohol 24 hours prior to the scan and were asked to fast 6 hours prior. Their blood glucose was checked just prior to an injection of 10 mCi FDG F18 (± 10%). The glucose level was confirmed per protocol. Patients were placed in a dark, quiet room for 30 min prior to injection and were then instructed to rest for 30 min after they were injected. Patients were taken to the restroom to empty their bladder on the way to the scanner. The scan was acquired on a 16-slice GE Discovery STE PET/CT scanner. Patients were placed in a supine position on the scan table with their head in a head cradle. The time interval between injection and scanning is 30–60 min. Scanning time was approximately 20 min. Acquisition parameters: transmission scan were the CT scan; 1 bed position; matrix size was 128 × 128. For the CT scan, the following parameters were applied: Topogram: 10 mAs 120 kVp/ CT mA 260, kVp 140/Slices 47. 3.75-mm thickness: Reconstruction parameters: Type of reconstruction: OSEM: iterations-2, Subsets 20; Processing filter: Gaussian, Setting 8.0: Slice Thickness 0.33 cm. The CT and attenuation corrected images were sent to the radiologist for interpretation.

All the statistical and image processing were done with statistical parametric mapping (SPM12, Wellcome Department of Cognitive Neurology Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) in MATLAB (MathWorks Inc., Sherborn, MA). The attenuation-corrected FDG-PET images were acquired for all 24 scans, three (one at baseline, one at tonic, and one at burst) for each subject. Initially, the binary mask of cerebellar cortex was extracted manually for every scan. All the FDG-PET images were normalized for intensity using the average uptake of the cerebellar cortex. The scans taken after the baseline (tonic and burst stimulation) were spatially coregistered onto the baseline PET image with 12-degrees-of-freedom linear transformation.

The intensity-normalized and coregistered images were spatially normalized onto the standard T1 Montreal Neurological Institute (MNI) template (voxel size = 2 × 2 × 2 mm^3, dimension = 91 × 109 × 91)

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Table 2. Individual and Average Score at Baseline, Tonic Stimulation, and Burst Stimulation for the Visual Analogue Scale (VAS) and the Pain Vigilance and Awareness Questionnaire (PVAQ).

Subject	Randomization	Baseline		Tonic		Burst	
		VAS	PVAQ	VAS	PVAQ	VAS	PVAQ
1	burst → tonic	80	26	24.5	19	49	12
2	tonic → burst	87	48	56	52	58	37
3	burst → tonic	92	25	7	47	36	40
4	burst → tonic	89	56	76	51	74	46
5	tonic → burst	80	49	21	49	21	13
6	tonic → burst	81	58	76	58	72	54
7	burst → tonic	79	42	80	44	64	38
Average		84.0	43.4	48.6	45.7	53.4	34.3

using 12-degrees-of-freedom linear transformation and smoothed with a Gaussian kernel of 8 mm full-width-half-maximum (FWHM). All the images were explicitly masked by the binary mask of T1 MNI template to exclude any activity outside the brain. For the group difference in activity level, a one-way ANOVA within subject design was used with no overall grand mean scaling. Each T-contrast between pairs was applied on baseline vs. burst, baseline vs. tonic, and burst vs. tonic, and the statistically significant voxels were found at uncorrected $p < 0.01$.

In addition, we also analyzed the difference in the activity level between conditions and compared it across groups, which were divided by subjects receiving either tonic or burst stimulation for the first 12 weeks. The images that were explicitly masked with *Montreal* Neurological Institute mask (this mask is a space that merely defines the boundaries around the brain, expressed in millimeters, from a set origin) were subtracted between conditions to be compared using an independent *t*-test. The pain sensation scores (i.e., VAS and PVAQ) were also subtracted between conditions to analyze in a multiple regression analysis. Initially, the activity difference between conditions was compared across tonic followed by burst (i.e., tonic-burst) or burst followed by tonic subjects (i.e., burst-tonic). Then, the tonic conditions and burst conditions were each compared using an independent *t*-test (significant at uncorrected $p < 0.01$). The results represent how the change in the metabolic activity between conditions differs depending on the order of stimulation type. The activity difference was also correlated to the changes in pain scores to show if change in activity can predict an increase or decrease in pain sensation level, correlating behavioral measures to changes on the molecular level.

RESULTS

Clinical Outcomes

On the VAS for pain, an average reduction of 41.5% (SD = 34.3) was obtained for tonic stimulation and an average reduction of 36.2% (SD = 21.8) was found for burst stimulation in comparison to baseline. A comparison between tonic and burst stimulation for the VAS pain showed a suppression of 14.4% (SD = 34.3%) for tonic stimulation compared to bust stimulation. For PVAQ, an increase of 9.3% (SD = 33.9) was demonstrated for tonic stimulation and reduction of 17.8% (SD = 39.0) for burst stimulation in comparison to the baseline measurement, while between tonic and burst stimulation a reduction of 26.3% (SD = 21.7) was obtained for burst stimulation compared to tonic stimulation. The individual and average scores for baseline, tonic, and burst stimulation for the VAS and PVAQ can be found in Table 2. It is interesting that PVAQ was increased for tonic stimulation in comparison to baseline. It is however important to note that this effect could be explained by mainly one participant (subject #3) that had a significant increase on the PVAQ. Interestingly, you see an opposite effect for the same subject for VAS (Table 1). It is however not clear why this patient has such a significant drop on the VAS.

Imaging Data

The Effects of Tonic and Burst Stimulation

A comparison between baseline and both tonic activity and burst activity stimulation showed a significant increase in metabolic rate in the premotor cortex. A significant increase in metabolic rate was also

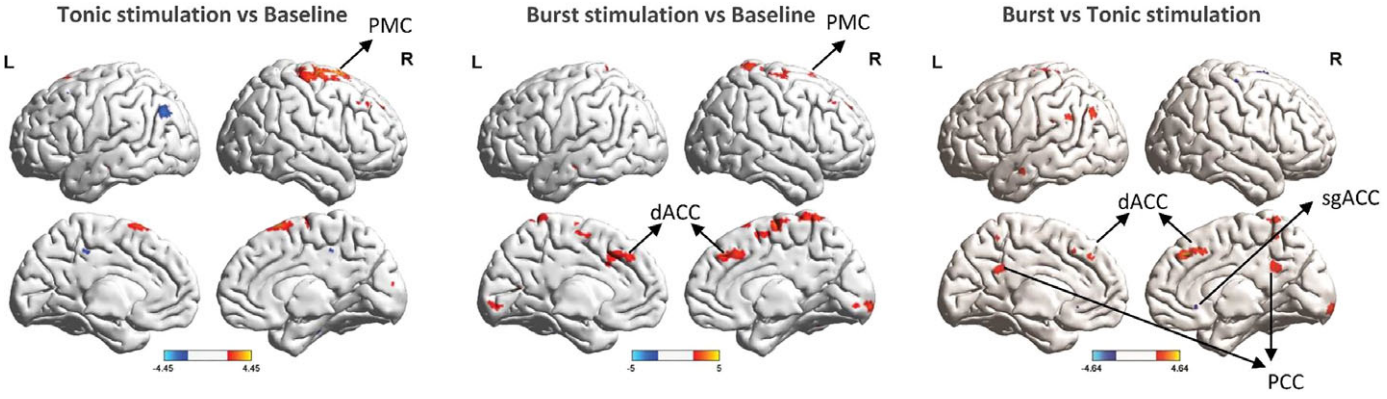

Figure 2. Left panel: Significant change in metabolic rate between tonic and baseline, Mid panel: Significant change in metabolic rate between burst and baseline, Right panel: Significant change in metabolic rate between burst and tonic activity. PMC, premotor cortex; dACC, dorsal anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; PCC, posterior cingulate cortex. [Color figure can be viewed at wileyonlinelibrary.com]

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observed in the dorsal anterior cingulate cortex during burst stimulation when compared to baseline activity. There was a significant increase in metabolic rate during burst stimulation when compared to tonic stimulation in the anterior cingulate cortex, and posterior cingulate cortex, as well as a decreased metabolic rate in the subgenual anterior cingulate cortex activity. Figure 2 and Table 3 show an overview.

A Regression Analysis With the VAS and PVAQ for Metabolic Changes

Tonic vs. baseline: A regression analysis between the VAS for pain and the metabolic changes between tonic stimulation and baseline showed a negative correlation between the VAS and a decreased metabolic rate for the retrosplenial and motor cortices extending into the supplementary motor cortex. These latter findings suggest that

Table 3. Overview of PET Results

Contrast	Region	Hemisphere	*t* value
Tonic <> Baseline	Posterior cingulate cortex	R	4.82
	Primary visual cortex	R	4.67
	Posterior cingulate cortex	L	4.61
	Angular gyrus	L	4.12
	Premotor	R	3.20
	Premotor	L	3.11
Burst <> Baseline	Premotor	R	4.84
	Precuneus	R	4.74
	Dorsal anterior cingulate cortex	L	4.66
	Precuneus	L	4.60
	Dorsal anterior cingulate cortex	R	4.51
	Primary visual cortex	L	3.41
	Primary visual cortex	R	3.20
Burst <> Tonic	Posterior cingulate cortex	L	4.27
	Dorsal anterior cingulate cortex	R	4.11
	Posterior cingulate cortex	R	4.08
	Dorsal anterior cingulate cortex	L	3.72
	Subgenual anterior cingulate cortex	R	3.72
	Primary visual cortex	R	3.54
	Angular gyrus	L	3.42
Tonic <> Baseline: VAS	Motor cortex	R	12.41
	Supplementary motor cortex	L	10.78
	Retrosplenial cortex	L	10.11
	Retrosplenial cortex	R	9.54
	Middle temporal lobe	L	9.46
Tonic <> Baseline: PVAQ	Retrosplenial cortex	L	10.41
	Middle temporal lobe	R	10.16
	Motor cortex	L	9.84
	Motor cortex	R	9.78
	Middle temporal lobe	L	9.74
	Retrosplenial cortex	R	9.71
	Thalamus	R	9.31
	Superior temporal lobe	R	8.45
Burst <> Baseline: VAS	None		
Burst <> Baseline: PVAQ	Visual cortex	L	9.45
	Subgenual anterior cingulate cortex	R	8.45
	Subgenual anterior cingulate cortex	L	8.39
Burst <> Tonic: VAS	Ventral medial prefrontal cortex	R	10.82
	Dorsal lateral prefrontal cortex	L	10.41
	Retrosplenial cortex	L	9.73
	Ventral thalamus	R	9.67
	Retrosplenial cortex	R	9.56
	Precuneus	L	9.11
	Dorsal anterior cingulate cortex	R	9.08
	Precuneus	R	9.05
	Dorsal anterior cingulate cortex	L	8.87
Burst <> Tonic: PVAQ	Precuneus	R	10.41
	Precuneus	R	10.37
	Ventral posterior thalamus	R	9.88
	Amygdala	R	9.82
	Motor cortex	R	8.74
	Motor cortex	L	8.55

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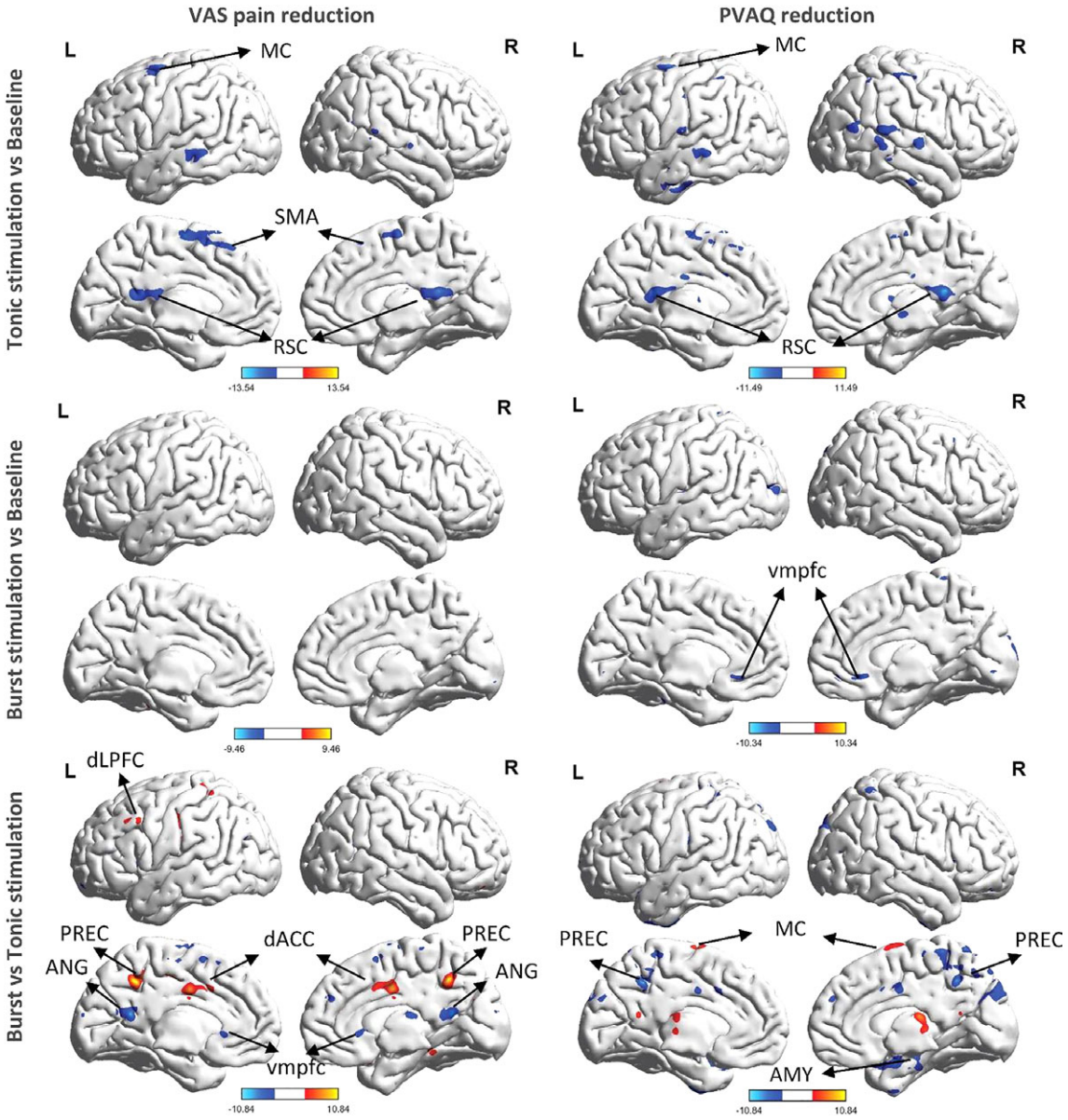

Figure 3. Left: Regression analysis between the visual analogue scale (VAS) for pain and the metabolic rate when comparing, tonic stimulation versus baseline, burst stimulation versus baseline, and burst versus tonic stimulation. Right: Regression analysis between the pain vigilance and awareness questionnaire (PVAQ) and the metabolic rate when comparing, tonic stimulation versus baseline, burst stimulation versus baseline, and burst versus tonic stimulation. PC, motor cortex; SMA, supplementary motor area; RSC, retrospenial cortex; dACC, dorsal anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; PCC, posterior cingulate cortex; PREC, precuneus; VMPFC, ventral medial prefrontal cortex; ANG, angular gyrus; dLPFC, dorsal lateral prefrontal cortex. [Color figure can be viewed at wileyonlinelibrary.com]

the higher the pain suppression on burst, the more decreased metabolic rate will be in the retrosplenial cortex and motor cortex extending into the supplementary motor cortex. A regression between the PVAQ and the metabolic rate between tonic stimulation and baseline shows a negative correlation for the retrosplenial cortex, and the thalamus, suggesting that the higher the reduction on the PVAQ the lower the metabolic rate (Fig. 3 and Table 3).

Burst vs. baseline: A regression analysis for the VAS and the metabolic rate between burst stimulation and baseline showed no significant effects. However, a regression analysis for the PVAQ and VAS and the metabolic rate between burst stimulation and baseline revealed an effect such that the higher the reduction on the PVAQ was, the lower the metabolic rate was in the ventromedial prefrontal cortex/subgenual anterior cingulate cortex (Fig. 3 and Table 3).

Burst vs. tonic: A regression analysis for the VAS for pain and the metabolic changes between burst and tonic stimulation showed a significant effect. A VAS for pain reduction was shown to correspond to an increased metabolic rate in the dorsal anterior cingulate cortex, the precuneus, and the dorsal lateral prefrontal cortex. This suggests that the higher the pain suppression with burst stimulation, the larger the increase will be in the metabolic rate of the dorsal anterior cingulate cortex, the precuneus, and the dorsal lateral prefrontal cortex in comparison to tonic stimulation. In addition, the regression analysis revealed that a VAS for pain (= burst – tonic) suppression showed a decrease in

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metabolic rate in the angular gyrus, the ventral medial prefrontal cortex, and the ventral lateral thalamus. A similar analysis for the PVAQ and the metabolic changes between burst and tonic stimulation demonstrated a direct correlation between the PVAQ and metabolic activity in the motor cortex and the ventral posterior thalamus. This suggests that the higher the PVAQ reduction with burst stimulation, the higher the increase in metabolic rate in the motor cortex and the ventral posterior thalamus compared to tonic stimulation. In addition, the regression analysis demonstrated PVAQ reduction and a decreased metabolic rate in the amygdala and the precuneus (Fig. 3 and Table 3).

DISCUSSION

The FDG-PET results of this study suggest that burst stimulation appears to exert a different pattern of brain activation, relative to tonic, in the lateral and medial pain pathways that are, respectively, involved in processing the sensory and emotional components of pain. This suggests an inherent difference in the central neural mechanisms during burst and tonic stimulation, which could potentially alter the patient's perception of pain. Yet, it is also possible that the effect obtained is not a direct sign of changes in pain perception but rather a difference in pain modulation by burst stimulation in comparison to tonic stimulation. However, this latter hypothesis can not explain the association between the change in PVAQ and VAS and the difference between tonic and burst stimulation. Indeed, when comparing brain metabolism differences between burst and tonic SCS, burst SCS seems to modulate the dorsal anterior cingulate cortex and posterior cingulate cortex (PCC) more than tonic stimulation. The difference in the dorsal anterior cingulate cortex was the main finding of the first EEG analysis between burst and tonic SCS (10). The dorsal anterior cingulate cortex is involved in the medial pain pathway, processing the affective, motivational control of pain, as clearly demonstrated by frontal lobotomies (25), cingulotomies (26), implanted electrodes in the dorsal anterior cingulate cortex for pain (27), and emotional modulation of pain (19). In essence, suppressing dorsal anterior cingulate cortex activity removes the salience from the pain (28,29). Thus the dorsal anterior cingulate cortex, as a part of the salience network, is critically involved in paying attention to the pain (30). Activity in the dorsal anterior cingulate cortex correlates with the amount of pain improvement, as measured by the VAS, when comparing burst with tonic stimulation and this relationship holds true inversely in the PCC. It is of interest that the difference in PVAQ is not related to the dorsal anterior cingulate cortex, as shown in a previous functional imaging study (10). Burst SCS further modulated the posterior cingulate cortex (PCC) reflected in brain metabolism differences between burst and tonic SCS in this brain area. This finding is inline with the EEG study of De Ridder and colleagues (10) and is not unexpected. The PCC has been associated to pain rumination and is involved in pain perception via the default mode network (30). The default mode network, apart from its posterior cingulate cortex hub, also involves the pregenual anterior cingulate cortex, which is a part of the opioidergic (31), serotoninergic, and dopaminergic (32) descending pain inhibitory pathway (33). Accordingly, activating the default mode network has an antinociceptive effect (30). In a more elaborate EEG analysis on the commonalities between burst and tonic firing in the study of De Ridder and Vanneste (34), the PCC was involved in both SCS designs (16). This was calculated by a conjunction analysis. This does not exclude that one stimulation design exerts a more pronounced effect on the posterior cingulate cortex, which can theoretically show up as a difference in metabolic activity. Based on a general heuristic model, it has been proposed that the function of the posterior cingulate cortex in pain is to reset the reference or set point via its connections to the dorsal anterior cingulate cortex (35). The dorsal anterior cingulate cortex encodes the acquisition of more pain input, while the pregenual anterior cingulate cortex encodes the suppression of further pain input (36). According to this model, the perception of pain is the result of a balance between pain provoking (dorsal anterior cingulate cortex and somatosensory cortex) and pain suppressing (pregenual anterior cingulate cortex) brain activity, which falls under the influence of the self-referential function of the posterior cingulate cortex (37).

Limitations of this PET study is the small number of patients enrolled to this particular site of the SUNBURST study and the fact that patients only had one session of data acquisition. Even with these caveats, the FDG-PET data seem to confirm the previous electrophysiological findings that support burst stimulation having a larger impact on the medial pain pathway than tonic stimulation, as demonstrated by its selective modulation of the dorsal anterior cingulate cortex. Larger studies should be performed to be able to extract more useful information from functional imaging with PET in the context of differentiating SCS designs. Furthermore, the studies using fMRI with a MRI compatible SCS burst device could further help to explain the underlying mechanism. Furthermore, the studies using fMRI with an MRI compatible SCS burst device could further help to explain the underlying mechanism.

Authorship Statement

Thomas Yearwood, Steven Falowski, and Lalit Venkatesan designed the study and collected the data. Hye Bin Yoo, Wing Ting To, and Sven Vanneste performed the data analysis. Dirk De Ridder, Wing Ting To, and Sven Vanneste wrote the manuscript. All authors approved the final version of the manuscript.

How to Cite this Article:

Yearwood T., De Ridder D., Yoo H.B., Falowski S., Venkatesan L., Ting To W., Vanneste S. 2019. Comparison of Neural Activity in Chronic Pain Patients During Tonic and Burst Spinal Cord Stimulation Using Fluorodeoxyglucose Positron Emission Tomography.
Neuromodulation 2019; E-pub ahead of print. DOI:10.1111/ner.12960

REFERENCES

1. Taylor RS, De Vries J, Buchser E, Dejongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. *BMC Cardiovasc Disord* 2009;9:13.
2. Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. *J Pain Symptom Manage* 2006;31:S13–S19.
3. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev* 2013;2:CD004001.
4. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. *Cochrane Database Syst Rev* 2004;3:CD003783.

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5. Hou S, Kemp K, Grabois MA. Systematic evaluation of burst spinal cord stimulation for chronic back and limb pain. *Neuromodulation* 2016;19:398–405.
6. Deer TR, Thomson S, Pope JE, Russo M, Luscombe F, Levy R. International neuromodulation society critical assessment: guideline review of implantable neurostimulation devices. *Neuromodulation* 2014;17:678–685. discussion 685.
7. Slavin KV, North RB, Deer TR, Staats P, Davis K, Diaz R. Tonic and burst spinal cord stimulation waveforms for the treatment of chronic, intractable pain: study protocol for a randomized controlled trial. *Trials* 2016;17:569.
8. Melzack R, Wall PD. Pain mechanisms—a new theory. *Science* 1965;150: 971–978.
9. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. *World Neurosurg* 2013;80:642–649. e641.
10. De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. *Neurosurgery* 2010;66: 986–990.
11. Courtney P, Espinet A, Mitchell B et al. Improved pain relief with burst spinal cord stimulation for two weeks in patients using tonic stimulation: results from a small clinical study. *Neuromodulation* 2015;18:361–366.
12. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. *Neuromodulation.* 2014;17:443–450.
13. de Vos CC, Bom MJ, Vanneste S, Lenders MW, de Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. *Neuromodulation* 2014;17:152–159.
14. Elgoyhen AB, Langguth B, De Ridder D, Vanneste S. Tinnitus: perspectives from human neuroimaging. *Nat Rev Neurosci* 2015;16:632–642.
15. Rinaldi PC, Young RF, Albe-Fessard D, Chodakiewitz J. Spontaneous neuronal hyperactivity in the medial and intralaminar thalamic nuclei of patients with deafferentation pain. *J Neurosurg* 1991;74:415–421.
16. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. *Neuromodulation* 2016;19:47–59.
17. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 2002;3:655–666.
18. Price DD. Neuroscience—psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288:1769–1772.
19. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci* 2013;14:502–511.
20. De Ridder D, Lenders MW, De Vos CC et al. A two center comparative study on tonic versus burst spinal cord stimulation: amount of responders and amount of pain suppression. *Clin J Pain* 2015;5:433–437.
21. De Ridder D, Plazier M, Menovsky T, Kamerling N, Vanneste S. C2 subcutaneous stimulation for failed back surgery syndrome: a case report. *Neuromodulation.* 2013;16:610–613.
22. De Ridder D, Vancamp T, Lenders MW, De Vos CC, Vanneste S. Is preoperative pain duration important in spinal cord stimulation? A comparison between tonic and burst stimulation. *Neuromodulation.* 2015;18:13–17.
23. Van Havenbergh T, Vancamp T, Van Looy P, Vanneste S, De Ridder D. Spinal cord stimulation for the treatment of chronic back pain patients: 500-Hz vs. 1000-Hz burst stimulation. *Neuromodulation* 2015;18:9–12. discussion 12.
24. Roelofs J, Peters ML, McCracken L, Vlaeyen JW. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain* 2003;101:299–306.
25. Freeman W, Watts JW. *Psychosurgery*. 2nd ed. Springfield, IL: Charles C Thomas, 1950.
26. Wilkinson HA, Davidson KM, Davidson RI. Bilateral anterior cingulotomy for chronic noncancer pain. *Neurosurgery* 1999;45:1129–1134.
27. Boccard SG, Pereira EA, Moir L et al. Deep brain stimulation of the anterior cingulate cortex: targeting the affective component of chronic pain. *Neuroreport* 2014; 25:83–88.
28. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. *Prog Neurobiol* 2011;93:111–124.
29. Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the "pain matrix". *Neuroimage* 2011;54: 2237–2249.
30. Kucyi A, Davis KD. The dynamic pain connectome. *Trends Neurosci* 2015;38: 86–95.
31. Fields H. State-dependent opioid control of pain. *Nat Rev Neurosci* 2004;5: 565–575.
32. Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. *Nat Rev Rheumatol* 2013;9:654–664.
33. Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL. Exploring the brain in pain: activations, deactivations and their relation. *Pain* 2010;148:257–267.
34. De Ridder D, Vanneste S. Does tonic spinal cord stimulation really influence the medial pain system? *Neuromodulation* 2016;19:227.
35. De Ridder D, Manning P, Glue P, Cape G, Langguth B, Vanneste S. Anterior cingulate implant for alcohol dependence: case report. *Neurosurgery* 2016;78: E883–E893.
36. De Ridder D, Vanneste S. Occipital nerve field transcranial direct current stimulation normalizes imbalance between pain detecting and pain inhibitory pathways in fibromyalgia. *Neurotherapeutics* 2017;2:484–501.
37. Knyazev GG. EEG correlates of self-referential processing. *Front Hum Neurosci* 2013;7:264.

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