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Potential Therapeutic Effect of Low Amplitude Burst Spinal Cord Stimulation on Pain

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Background: The SUNBURST Study, a USA-based controlled cross-over trial demonstrated that burst spinal cord stimulation was superior compared to tonic stimulation in suppressing chronic intractable pain. However, when on burst stimulation, participants preferred lower to higher amplitudes. This led to the hypothesis that lower burst amplitudes will correlate with lower pain scores while higher amplitudes will be associated with higher pain scores.

Objective: To investigate correlations between burst amplitude and self-reported pain and different psychosocial measures.

Materials and Methods: One hundred participants in the SUNBURST study were randomized to receive burst or tonic stimulation, each for 12 weeks in a cross-over manner. Complete data of 99 participants were used in this secondary analysis. Pearson correlations were conducted at 6-, 12-, 18-, and 24-weeks postactivation to determine the strength of linear relationships between burst amplitude and (1) the average seven-day daily pain Visual Analogue Scale (VAS), (2) the different domains of the Pain Catastrophizing Scale (PCS), (3) the different domains of the SF-36v2 (Quality Metric Incorporated, Lincoln, RI) Health Survey. In addition, correlations between tonic stimulation amplitude and the above-mentioned outcome measures were examined.

Results: Significant positive correlations were identified between burst amplitude and total, "worst," and "trunk" pain for VAS; all domains for PCS; and "Role-Physical," "Bodily Pain," and "General Health" for SF-36v2™ after 12-weeks of burst stimulation.

Conclusions: In burst spinal cord stimulation, in contrast to tonic stimulation, lower amplitudes are more effective in suppressing pain than high amplitudes.

Keywords: Amplitude, burst, burst stimulation, parameter, spinal cord stimulation

Conflict of Interest: Sook Ling Leong has no conflicts of interest to declare. Dirk De Ridder has patent for burst stimulation. Timothy Deer serves as a paid consultant for Abbott (formerly St. Jude Medical), Axonics, Bioness, Saluda Medical, Spinethera, and Vertos Medical. Sven Vanneste has no conflicts of interest to declare.

INTRODUCTION

Chronic, intractable pain has been routinely treated by tonic electrical stimulation (Fig. 1A) of the spinal cord (1). Spinal cord stimulation (SCS) is thought to be based on the "gate–control" theory (2), which postulates that activity in large diameter cutaneous fibers (type Aβ) inhibits the transmission of noxious information via small Aδ and unmyelinated C fibers to the brain. Randomized controlled studies have demonstrated the efficacy and safety of tonic SCS in pain management (3). However, the benefits of traditional SCS are limited, with approximately 50% of patients reporting insufficient pain relief, and a frequent progressive tolerance affecting SCS's long-term efficacy (4,5). In addition, in tonic SCS, paresthesia is inevitable and may be mandatory for obtaining successful pain relief (3,5).

The development of burst stimulation (Fig. 1B), a concept inspired by the dual firing (ie, tonic and burst) properties of thalamic cells permits effective paresthesia-free stimulation (6,7). The first pilot study in 2010 reported an enhanced clinically meaningful reduction for axial and limb pain, with sustained improvements in pain affect (eg, tiring, exhausting, sickening) and sensory (eg, throbbing, shooting, stabbing) measurements after one year for burst in contrast to tonic stimulation (8). Moreover, paresthesia was present in only 17% of patients during burst compared to 92% during tonic stimulation. The augmented therapeutic effects of burst compared to tonic stimulation were subsequently replicated in several moderate sized clinical studies (9–13).

Recently, a large, 100 participants, controlled clinical trial was conducted to examine the safety and efficacy of burst stimulation (14). The Success Using Neuromodulation with BURST (SUNBURST) study was designed using the cross-over model to establish non-inferiority in pain intensity for burst stimulation when evaluated against tonic stimulation. Results indicated that

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besides being non-inferior to tonic stimulation, superiority was attained. Also, study findings revealed that a larger percentage of participants preferred burst stimulation, with over 90% indicating decreased paresthesia.

During the implementation of the SUNBURST study, although not documented, verbal feedback from participants suggested that lower as opposed to higher burst amplitudes were more effective for pain relief. In addition, interim analysis of an ongoing substudy of the SUNBURST, yet to be published, showed that participants reported favorably to amplitudes below compared to above the standard 1.45 mA. This led to the hypothesis that burst spinal cord stimulation could be different from tonic stimulation in that lower amplitudes may be more beneficial than higher amplitudes. It is noteworthy that the mechanism of burst stimulation is not completely understood. Studies have suggested that at a system level, burst in comparison to tonic modulates the medial pathway in addition to the lateral and descending pathways (13,15–17). At a cellular level, unlike tonic stimulation, burst is independent of the spinal GABAergic mechanisms (18).

Limited mechanistic knowledge and experience with the relatively new burst stimulation design advocates the need to consider the possibility that lower compared to higher burst amplitudes may elicit a more prominent therapeutic effect. An awareness of this counterintuitive phenomenon is imperative in assisting with optimization of burst parameters for pain relief. Thus, utilizing data from the SUNBURST study, the primary objective of this study was to examine correlations between burst amplitude and self-reported pain as well as available psychosocial measures. Secondarily, we investigated the correlations between charge per pulse and charge per second with self-reported pain as well as available psychosocial measures. Also, we examined the correlations between tonic amplitudes, charge per pulse, and charge per second with self-reported pain and psychosocial measures.

METHOD

Study Cohort

The Success Using Neuromodulation with BURST (SUNBURST) study was a multicenter, randomized, cross-over, and unblinded trial investigating the safety and efficacy of burst compared to tonic spinal cord stimulation (SCS) for the treatment of chronic, intractable pain in the limbs and trunk (14,19). Features of the SUNBURST cohort and its design have been described in detail (14,19). Briefly, 100 participants who showed at least 50% self-reported overall pain intensity relief during a standard tonic stimulation trial were implanted with a rechargeable neurostimulation device that can deliver both tonic and burst stimulations. Subsequently, in the cross-over phase, participants were randomized to receive burst or tonic stimulation, each for 12 weeks. Complete data collected during the 24-week cross-over period were used, yielding a final sample of 99 participants (N = 54 for burst then tonic N = 45 for tonic then burst) at baseline for the present secondary analysis. This study was performed in accordance to the Helsinki Declaration standards and can be identified with the clinical trial identifier: NCT02011893.

Stimulation Parameters

Burst stimulation was programmed at 500 Hz per burst, delivered in groups of 5 spikes, set with a 1 millisecond pulse width and repeated at a frequency of 40 Hz. Tonic stimulation was delivered in the frequency ranges of 30 and 100 Hz with pulse widths from 100 to 500 μsec. To optimize stimulation parameters, burst and tonic amplitudes were modified as needed, during assessment or unscheduled clinic visits. Burst stimulation optimization was based on participants' perception (19). Data was collected only during assessment clinic visits. All participants were provided with the Patient Programmer, allowing them to turn the device ON and OFF, and to adjust the stimulation amplitude within a set range.

Electrical Charge Delivery

The amount of electrical charge per pulse (μC) was calculated by multiplying the amplitude with the pulse width. Subsequently, the electrical charge per second (mA) was derived by multiplying the electrical charge per pulse by frequency.

Primary Outcome Assessment

In this study, assessments at baseline, as well as 6-, 12-, 18-, and 24-weeks post-activation of stimulation device were included. Self-reported average daily "overall," "worst," "trunk," and "limb" pain were evaluated on a Visual Analogue Scale (VAS) for seven days prior to each clinic visit.

Secondary Outcome Assessments

The Pain Catastrophizing Scale (PCS) (20), completed at baseline, week-12 and week-24 post device activation appraised participants' thoughts and feelings during pain. In addition, the SF-36v2 Health Survey (21) completed at week 24 post-activation was used to assess quality of life.

Analyses

Two-sample *t*-tests were used to examine differences at baseline and 6-, 12-, 18-, and 24-weeks post-activation between Group A (burst then tonic) and Group B (tonic then burst). Within group, stimulation protocol differences were analyzed using paired t-tests. Also, two-sample *t*-tests were utilized to examine differences between burst and tonic amplitudes, charge per pulse, and charge per second at all-time points.

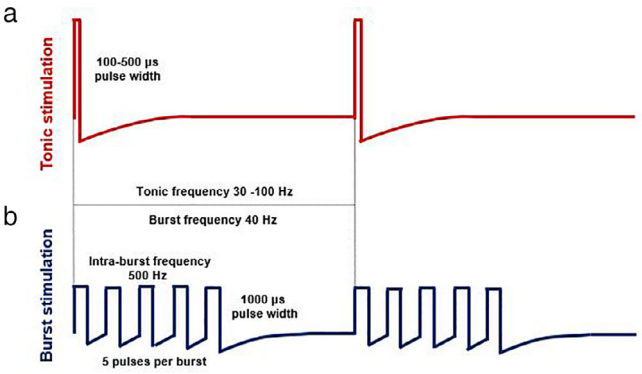

Figure 1. A, Tonic stimulation delivered in the frequency ranges of 30 and 100 Hz with pulse widths from 100 to 500 μsec. B, Burst stimulation programmed at 500 Hz per burst, delivered in groups of five spikes, set with a 1 msec pulse width and repeated at a frequency of 40 Hz. [Color figure can be viewed at wileyonlinelibrary.com]

Pearson's correlation was used to examine the strength of the linear relationship between amplitude and outcome measurements (Pain VAS, PCS) at each time-point cross-sectionally. It has been reported that carry over effect did not impact the results of the SUNBURST study (14), and given a positive significant correlation between amplitude and total VAS score at 12-weeks burst, data were pooled to examine the correlations between the combined burst amplitudes of both groups and the different domains of the VAS and PCS at week-12 burst stimulation (Group A, week-12 post-activation and Group B, week-24 post-activation). Furthermore, Pearson's correlation between the different domains of SF-36v2 and the combined 12-week burst stimulation amplitudes were investigated. The "physical functioning," "role-physical," and "role-emotional" domains of the SF-36v2 health survey were inversely scored in the present analyses. Results were deemed significant if $P < .05$. All statistical analyses were conducted using STATA 15.1.

RESULTS

Change in Outcome Measures

There were no significant differences in outcome measures between groups at baseline, 6-, 12-, 18-, and 24-weeks post-activation (Table 1). Akin to the SUNBURST study, within group analyses revealed clinically significant improvements for all VAS domains (ie, decrease of at least 30%). When comparing baseline to 6-, 12-, 18-, and 24-weeks post-activation (Table 1), there were no significant differences for all measures between 6- and 12-weeks for burst and 12-, 18-, and 24-weeks for tonic in Group A. Similarly, no significant changes were established for all measures between 6- and 12-weeks for tonic and 12-, 18-, and 24-weeks for burst in Group B (Table 1).

Electrical Charge Delivered

There were significantly lower burst mean amplitude (Fig. 2A) and mean charge per pulse (Fig. 2B) compared to tonic at 6-, 12-, 18-, and 24- weeks post-activation. However, the mean charge per second delivered to the spinal cord for burst stimulation was significantly higher at 12- and 18-weeks post-activation (Fig. 2A) compared to tonic.

Correlations for Pain Visual Analogue Scale (VAS)

At 12-weeks burst stimulation, both groups A and B were more likely to experience heightened "overall" and "worst" pain with higher amplitude (Fig. 3. a1"overall," a2"worst"), charge per pulse (Fig. 3. b1"overall," b2"worst") and charge per second (Fig. 3. c1"overall," c2" worst"). In addition, at 12-weeks burst, participants in group B were more likely to report higher scores for "limb" and "trunk" pain with higher amplitude (Fig. 3. a3"limb," a4"trunk"), charge per pulse (Fig. 3. b3"limb," b4"trunk") and charge per second (Fig. 3. c3"limb," c4"trunk"). In group A, at week-18, participants were more likely to experience less "worst" pain with higher

Table 1. Mean (SE) Scores of the Different Domains of the Pain Visual Analogue Scale (VAS) and the Pain Catastrophizing Scale (PCS) at each time-point for Groups A (burst then tonic) and B (tonic then burst).

Measures	Group A (n = 54)					Group B (n = 45)				
	Burst			Tonic		Tonic			Burst	
	Baseline[1]	Week 6[2]	Week 12[3]	Week 18[4]	Week 24[5]	Baseline[1]	Week 6[4]	Week 12[5]	Week 18[2]	Week 24[3]
	(n = 54)	(n = 47)	(n = 51)	(n = 48)	(n = 49)	(n = 45)	(n = 44)	(n = 45)	(n = 43)	(n = 45)
Pain VAS										
Overall, mean (SE)	75.33 (1.20)[a]	43.43 (3.42)[b]	43.46 (3.54)[b]	39.73 (3.45)[c]	43.68 (3.43)[c]	74.86 (1.21)[d]	43.59 (3.00)[e]	46.05 (3.27)[e]	39.99 (3.35)[f]	41.73 (3.95)[f]
Worst, mean (SE)	83.25 (1.21)[a]	52.70 (3.79)[b]	51.86 (3.78)[b]	48.36 (3.96)[c]	52.90 (3.74)[c]	83.02 (1.40)[d]	53.07 (3.20)[e]	55.39 (3.45)[e]	49.05 (3.65)[f]	51.51 (4.15)[f]
Limb, mean (SE)	73.62 (2.81)[a]	39.28 (3.78)[b]	33.71 (3.73)[b]	35.07 (3.75)[c]	37.94 (3.74)[c]	65.81 (3.47)[d]	36.83 (3.77)[e]	35.76 (3.52)[e]	34.38 (3.75)[f]	35.82 (4.15)[f]
Trunk, mean (SE)	76.33 (1.30)[a]	41.09 (3.60)[b]	40.60 (3.57)[b]	39.30 (3.78)[c]	41.35 (3.49)[c]	71.12 (2.55)[d]	44.35 (3.10)[e]	42.62 (3.08)[e]	37.25 (3.43)[f]	38.66 (3.75)[f]
Pain Catastrophizing Scale (PCS)										
Total, mean (SE)	19.41 (1.64)[a]		14.35 (1.55)[b]		11.54 (1.66)[c]	21.07 (1.76)[d]		12.78 (1.66)[e]		10.58 (1.63)[f]
Rumination, mean (SE)	8.19 (0.63)[a]		6.43 (0.66)[b]		5.2 (0.72)[c]	8.24 (0.69)[d]		5.27 (0.63)[e]		4.71 (0.68)[f]
Magnification, mean (SE)	3.13 (0.36)[a]		2.35 (0.32)[b]		1.88 (0.31)[c]	3.64 (0.39)[d]		2.27 (0.32)[e]		1.80 (0.36)[f]
Helplessness, mean (SE)	8.09 (0.78)[a]		5.57 (0.73)[b]		4.46 (0.79)[c]	9.18 (0.84)[d]		5.24 (0.83)[e]		4.07 (0.72)[f]

Two sample-test between groups A and B comparing:
[1, 1] = Baseline. [2, 2] = Week 6 of burst stimulation. [3, 3] = Week 12 of burst stimulation. [4, 4] = Week 6 of tonic stimulation. [5, 5] = Week 12 of tonic stimulation.

Paired *t*-test within group and stimulation parameters (Group A):
[a,b] = $P < .05$, comparing baseline and week 6; and baseline and week 12 of burst stimulation.
[b,b] = $P < .05$, comparing week 6 and week 12 of burst stimulation.
[a,c] = $P < .05$, comparing baseline and week 6; and baseline and week 12 of tonic stimulation.
[c,c] = $P > .05$, comparing week 6 and week 12 of tonic stimulation.

Paired *t*-test within group and stimulation parameters (Group B):
[d,e] = $P < .05$, comparing baseline and week 6; and baseline and week 12 of tonic stimulation.
[e,e] = $P > .05$, comparing week 6 and week 12 of tonic stimulation.
[d,f] = $P < .05$, comparing baseline and week 6; and baseline and week 12 of burst stimulation.
[f,f] = $P > .05$, comparing week 6 and week 12 of burst stimulation.

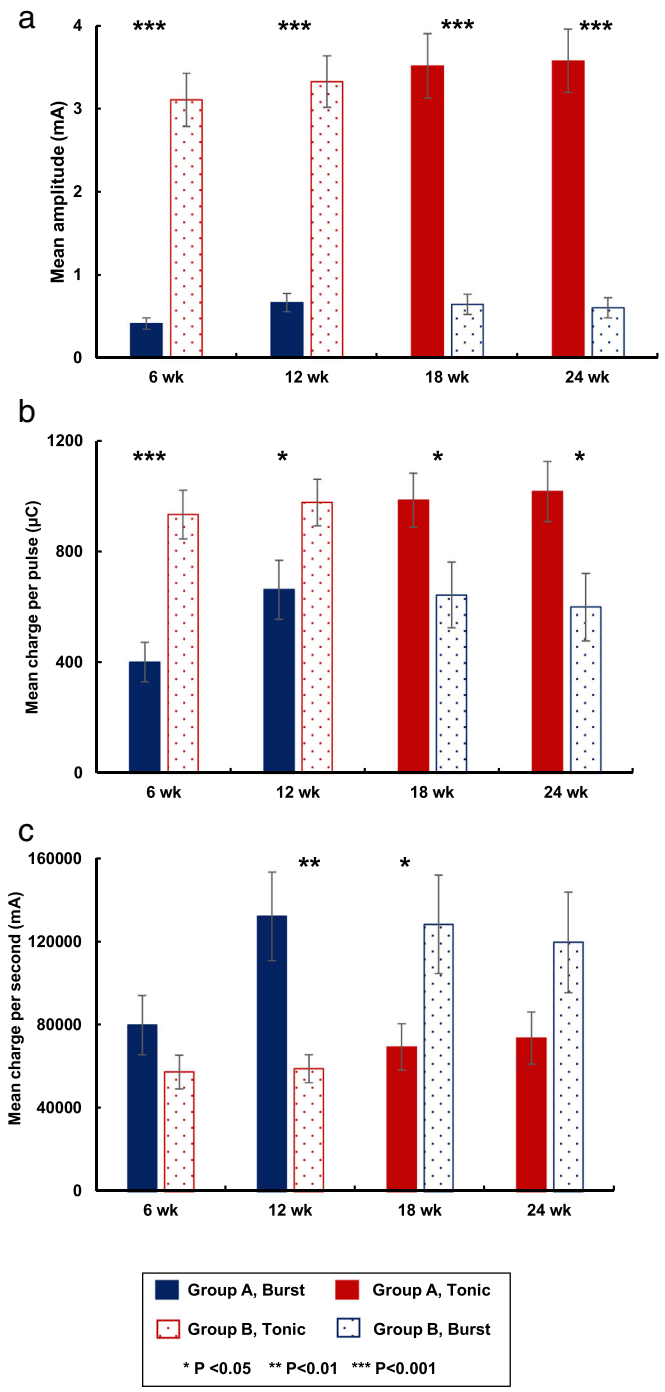

Figure 2. A, Mean amplitude (mA) for burst and tonic stimulations in groups A and B. B, Mean charge per pulse (μC) for burst and tonic stimulations in groups A and B. C, Mean charge per second (mA) for burst and tonic stimulations in groups A and B. [Color figure can be viewed at wileyonlinelibrary.com]

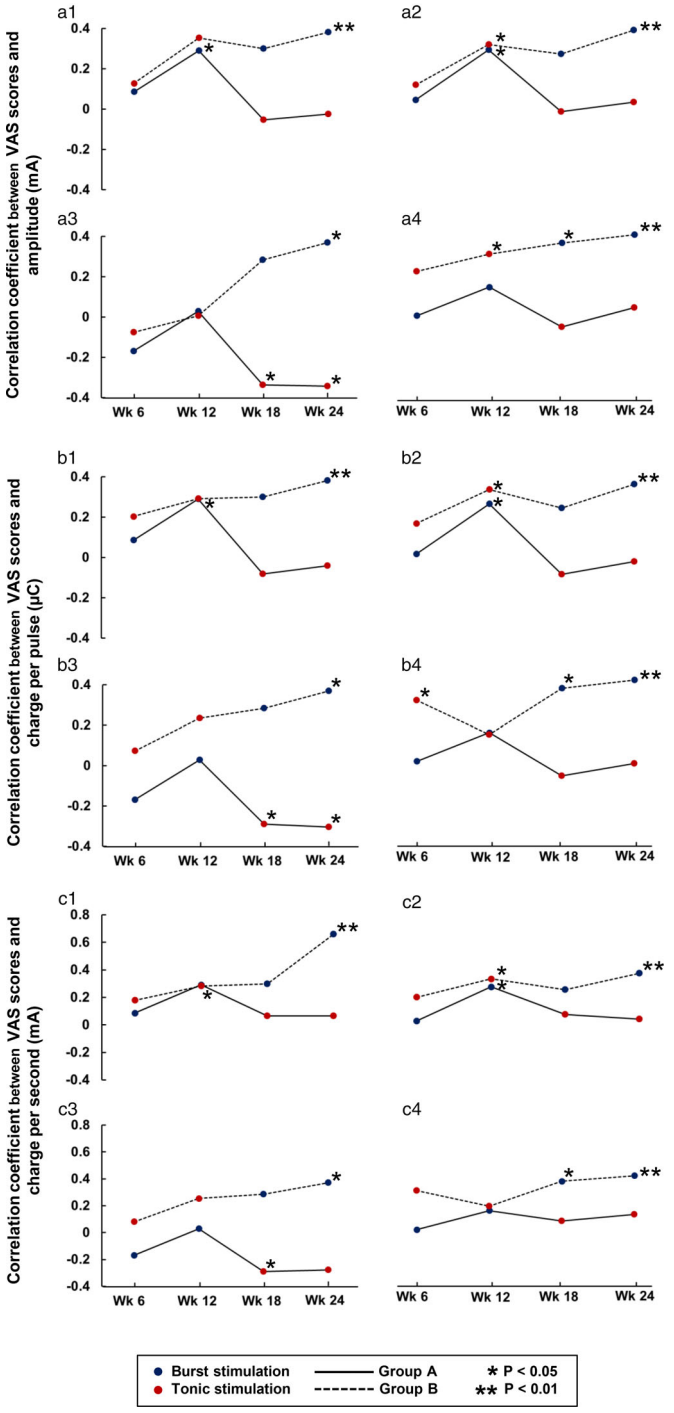

Figure 3. Pearson's correlation between amplitude and overall (a1), worst (a2), limb (a3), and trunk (a4) pain in groups A and B. Pearson's correlation between charge per pulse and overall (b1), worst (b2), limb (b3), and trunk (b4) pain in groups A and B. Pearson's correlation between charge per second and overall (c1), worst (c2), limb (c3), and trunk (c4) pain in groups A and B. [Color figure can be viewed at wileyonlinelibrary.com]

tonic amplitude (Fig. 3. a3), charge per pulse (Fig. 3. b3), and charge per second (Fig. 3. c3).

Correlations for Pain Catastrophizing Scale (PCS)

Results indicate that at 12-weeks of burst stimulation, with higher amplitude (Fig. 4. a1), charge per pulse (Fig. 4. b1) and charge per second (Fig. 4. c1), participants were more likely to experience further catastrophizing thoughts. Similar incremental results were established between "magnification," and "helplessness" with burst amplitude (Fig. 4. a3"magnification," a4"helplessness"), charge per pulse (Fig. 4. b3"magnification," b4"helplessness") and charge per second (Fig. 4. c3"magnification," c4"helplessness"). For group B, during tonic stimulation, participants observed elevated feelings of "helplessness" with higher charge per pulse (Fig. 4. b4) as well as

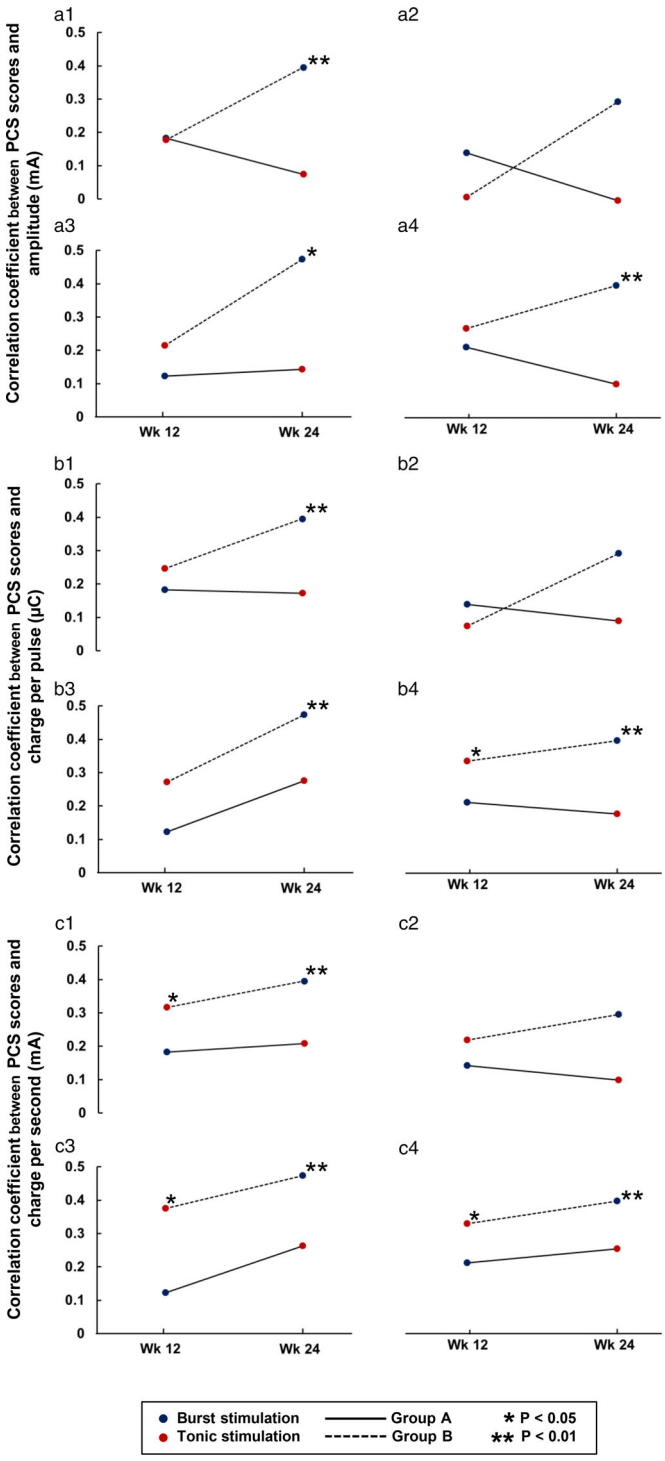

Figure 4. Pearson's correlation between amplitude and total (a1), rumination (a2), magnification (a3), and helplessness (a4) in groups A and B. Pearson's correlation between charge per pulse and total (b1), rumination (b2), magnification (b3), and helplessness (b4) in groups A and B. Pearson's correlation between charge per second and total (b1), rumination (b2), magnification (b3), and helplessness (c4) in groups A and B. [Color figure can be viewed at wileyonlinelibrary.com]

charge per second (Fig. 4. c4). In addition, in group B, at 12-week tonic stimulation, participants reported that they were more likely to magnify (Fig. 4. c3) the threat of pain with higher charge per second.

Correlations for Combined Burst With VAS, PCS, and SF-36v2™

Participants of the SUNBURST study indicated a higher likelihood of overall, "worst" and "trunk" pain on the combined VAS with increases in burst stimulation amplitude (Fig. 5. a1), charge per pulse (Fig. 5. b1), and charge per second (Fig. 5. c1). Correspondingly, with higher burst amplitude (Fig. 5. a2), charge per pulse (Fig. 5. b1), and charge per second (Fig. 5. c2), the tendency to catastrophize, magnify, and feel helpless were more likely to ensue. Study results also showed that higher burst amplitude (Fig. 5. a3), charge per pulse (Fig. 5. b3), and charge per second (Fig. 5. c3) were associated with negative outcomes of the SF-36v2™ domains.

DISCUSSION

This is the first study to demonstrate positive correlations between burst amplitude and self-reported pain scores measured on the VAS, as well as psychosocial measures using PCS and SF-36v2. Although clinically meaningful differences in pain scores between lower and higher burst stimulation need to be addressed by a longitudinal study, current results suggest that lowering burst SCS amplitude can improve pain suppression, while increasing the amplitude will worsen pain. One reason, as demonstrated in the results of this study, is that a significantly higher amount of electrical current is delivered per second to the spinal cord at lower amplitudes using the burst design compared to tonic. Consistent with pain VAS score results, it is therefore not surprising that increasing the amplitude of burst stimulation is associated with adverse reactions to pain as measured by the different domains of PCS and SF-36v2. Although less apparent and consistent, there were significant positive correlations between tonic SCS amplitude and VAS, indicating that this principle may also hold some truth for tonic stimulation.

It has been demonstrated that in contrast to tonic stimulation which modulates the lateral pain pathway, burst stimulation exerts its effect predominantly through the medial pain pathway, thereby also altering the individual's attention towards pain and changes in pain (13,15,16,22). Thus, it is conceivable that the current results could be explained by the modulation of the medial pain pathway (23). To formally evaluate this proposition, future neuroimaging studies will have to be conducted.

It must be stressed that these findings are preliminary, derived from participants of the SUNBURST study. Nevertheless, the importance of the present study should not be underestimated as it can have both pathophysiological and clinical implications. Pathophysiologically, if proven longitudinally, these results could be explained by the inverted-U curve profile demonstrated in the dorsal anterior cingulate cortex (24). Considering the relatively high amplitudes applied in the SUNBURST study, it is likely that all amplitudes are in the downward deflection of an inverted-U curve profile.

Findings from this study also have practical clinical implications. The present results, if confirmed in future longitudinal studies, lead to counterintuitive programming, where suboptimal results can be improved by lowering the stimulation amplitude rather than by more intuitive increasing of the amplitude. Lowering the amplitude indeed demonstrated a clinical improvement in the interim analyses of the yet to be published SUNBURST optimization study. Pain suppression improved from 3.6 to 2.6 on the pain VAS when amplitudes were lowered from 1.4 to 0.6 mA. However, it is evident that the optimization of tonic stimulation on the other hand must primarily be guided by the individual's

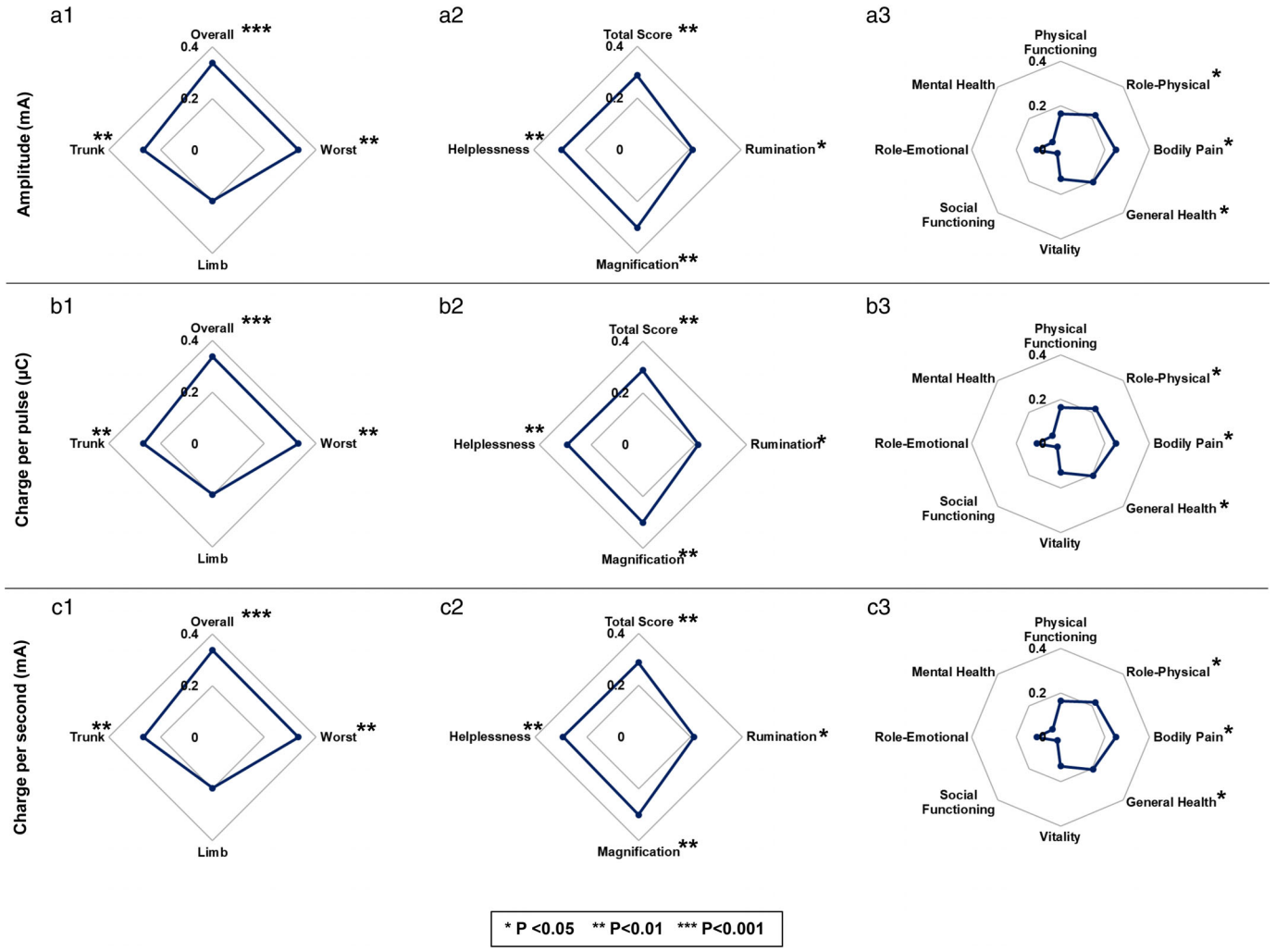

Figure 5. Pearson's correlation between the combined burst amplitude and different domains of the Pain Visual Analogue Scale (VAS) (a1), the different domains of the Pain Catastrophizing Scale (PCS) (a2), and the different domains of the SF36 (a3). Pearson's correlation between the combined burst charge per pulse and different domains of the Pain Visual Analogue Scale (VAS) (b1), the different domains of the Pain Catastrophizing Scale (PCS) (b2), and the different domains of the SF36 (b3). Pearson's correlation between the combined burst charge per second and different domains of the Pain Visual Analogue Scale (VAS) (c1), the different domains of the Pain Catastrophizing Scale (PCS) (c2), and the different domains of the SF36 (c3). [Color figure can be viewed at wileyonlinelibrary.com]

perception (amplitude first detectable) and discomfort threshold (paresthesia) (25), rendering any positive significant results of this study somewhat inconsequential.

As previously stated (14), the main limitation of the SUNBURST study is that it was not designed to determine the changes in pain from baseline to follow-up (ie, establish clinically important difference after treatment from baseline). Moreover, it is of note that all participants in the SUNBURST study were tonic responders, and due to the cross-over design, clinically important implications of burst-stimulation cannot be fully established. Also, it must be emphasized that this post-hoc analysis is cross-sectional in nature, thus incapable of determining clinically important differences on the VAS (at least 30% reduction), PCS, and SF-36.

Another limitation of this cross-sectional analysis is the inability of the model to predict whether higher burst amplitude led to higher self-reported pain VAS scores or *vice versa*. Further longitudinal studies designed specifically to test this hypothesis are required. Yet, correlational results would be consistent with a longitudinal model given that there is a slight but gradual positive increase between burst amplitude and outcome measures over time. Also, neuroimaging studies are needed to elucidate the potential mechanism of this phenomenon.

In conclusion, secondary analyses of the SUNBURST study demonstrated the presence of a counterintuitive principle for burst SCS, in that lower amplitudes are superior to higher amplitudes. Well designed, longitudinal studies are needed to establish true causality. This concept agrees with another way of lowering the charge delivered to the spinal cord: cycling mode, where burst SCS is delivered with on and off periods. A first study has demonstrated that lowering the charge by cycling results in equally good pain suppression (26). This study, combined with data from micro dosing, (=cycling) suggest that practitioners programming burst SCS should consider lowering the amplitude, as it may have additional therapeutic effect.

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Authorship Statements

Sook Ling Leong and Sven Vanneste analyzed, interpreted, and prepared the manuscript draft. Dirk De Ridder and Timothy Deer interpreted and provided critical review of the manuscript. All authors approved the final manuscript.

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