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Burst and 10 kHz Spinal Cord Stimulation: Different and Common Brain Mechanisms

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ABSTRACT

Background: Spinal cord stimulation is routinely used to treat medically intractable pain. Different stimulation designs exist for pain suppression. Among these, both high-frequency stimulation at 10 kHz and burst stimulation are paresthesia-free, and it has been postulated, on the basis of theoretical and clinical grounds, that they may be fundamentally the same, ie, that both modulate the medial "suffering" pathway rather thantonic stimulation; yet no proof exists for this proposal.

Materials and Methods: Clinical and electroencephalographic (EEG) data from ten patients undergoing both burst with passive recharge and 10 kHz spinal cord stimulation for ten days are analyzed to examine the commonalities and differences between burst and 10 kHz stimulation. A source localized (standardized low-resolution brain electromagnetic tomography) EEG subtraction and conjunction analysis is performed in each condition.

Results: Burst and 10 kHz significantly reduced leg pain to a similar extent. For back pain, burst showed a substantial reduction from baseline, whereas 10 kHz did not; however, the direct comparison between burst and 10 kHz was not significant. Brain differences were observed in alpha-band activity within medial cingulate and operculo-insular regions during burst relative to 10 kHz, whereas both paradigms shared beta activity with a peak in the pregenual anterior cingulate region. Given the 19-channel montage, these anatomic assignments should be interpreted cautiously. Burst and 10 kHz stimulation share beta activation in the pregenual anterior cingulate cortex (pgACC). The common pgACC activation correlates with the degree of pain suppression in both the back and the legs. The dorsal anterior cingulate cortex deactivation correlates with back pain reduction in burst. For 10 kHz, there is no significant correlation.

Conclusions: These data suggest that burst and 10 kHz stimulation both modulate the descending pain-inhibitory system (through pgACC), thereby decreasing both back and leg pain. Burst also modulates the dorsal anterior cingulate cortex, subgenual anterior cingulate cortex, and insula, which correlate with changes in back pain.

Keywords: 10 kHz, burst, EEG, spinal cord stimulation, tonic

INTRODUCTION

Spinal cord stimulation (SCS) is an established therapy for chronic neuropathic pain refractory to conservative management. Since 2010,[1] waveform innovation has expanded beyond conventional tonic stimulation, resulting in multiple paraesthesia-free stimulation paradigms. Among these, 10 kHz high-frequency stimulation[2,3] and burst stimulation (BurstDR)[4,5] are widely used because they outperform traditional tonic SCS.[6] Because both paradigms can achieve analgesia without paraesthesia and have similar clinical benefits for pain, suffering, and sleep, it has been proposed that they may share a common mechanism distinct from dorsal column paraesthesia-based gating, potentially involving modulation of supraspinal networks associated with the medial pain system and descending control.[7]

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Despite this hypothesis, direct mechanistic comparisons of 10 kHz and burst within the same patients are nonexistent. Most studies have evaluated these paradigms separately and across heterogeneous clinical conditions, limiting inference about shared versus stimulation-specific mechanisms. Electroencephalography (EEG), combined with source localization, can provide insight into stimulation-induced modulation of cortical networks relevant to chronic pain, including the lateral, medial, and descending pain pathways.[8–11]

The present study aimed to compare the clinical and EEG effects of 10 kHz and burst in a within-subject design and randomized participants to start with burst or 10 kHz to prevent an order effect. We analyzed pain outcomes and source-localized EEG changes in patients receiving both stimulation paradigms for ten days each. Using standardized low-resolution brain electromagnetic tomography (sLORETA) subtraction and conjunction analyses, we sought to identify shared cortical signatures and paradigm-specific modulation. Finally, we assessed the relationship between EEG changes and clinical pain relief to determine whether cortical signatures track analgesic response.

MATERIALS AND METHODS

Study Design and Setting

This was a single-center, prospective, randomized, double-blind, crossover pilot study conducted at The Leeds Teaching Hospitals NHS Trust (Pain & Neuromodulation Centre, Leeds, UK). Participants undergoing SCS implantation for failed back surgery syndrome. Participants received both 10 kHs and BurstDR—in randomized order—with EEG used to compare brain activation patterns across conditions.

Participants

1. Eligibility criteria

Adults (≥18 years) were eligible if they had chronic predominant neuropathic low back pain (with or without radiculopathy) for ≥six months following prior spinal surgery (>six months prior), baseline visual analogue scale (VAS) for back pain ≥five, neuropathic pain confirmation in line with NICE TAG 0159, and a total daily opioid dose ≤200 mg morphine equivalent. Participants were required to be willing and able to comply with study procedures, including EEG acquisition.

Key exclusions included mechanical spinal instability, pregnancy, epilepsy, implanted cardiac devices that would preclude implantation, morbid obesity (body mass index ≥40), significant comorbidity precluding surgery, inability to complete questionnaires or use the programmer, concurrent trial participation within 30 days, spinal fracture, tumor, or infection, cauda equina syndrome, progressive neurologic deficit, and epilepsy.

2. Recruitment, screening, and consent

Potential participants were identified from the theatre waiting list for the SCS trial with a diagnosis of failed back surgery syndrome. After provision of written and verbal study information, eligibility was confirmed, and the investigator team obtained written informed consent. Each participant was assigned a unique study identification number; participation was documented in medical notes, and the participant's GP was notified per site procedures.

A total of 19 patients consented and completed baseline assessments; one subsequently withdrew consent, leaving 18 patients who were randomized equally between two arms (nine per arm). Arm A received 10 kHz followed by BurstDR trial ten days each, and Arm B received burst followed by 10 kHz. In Arm A, one patient experienced a trial failure, and one had no EEG data obtained, leaving seven patients with evaluable data. In Arm B, two patients withdrew, two had trial failures, and one had incomplete data, resulting in four patients with complete data sets. Overall, data were available for 11 patients. Data cleaning excluded one patient. The study was discontinued due to the COVID-19 pandemic, during which trial procedures were halted in the unit and patients proceeded directly to permanent implantation. Among the 11 patients (seven female, four male; mean age 50.0 ± 10.35 years) with available data, two (18%) showed a negative trial response to 10 kHz, whereas five (45%) showed a negative response to BurstDR (Fig. 1). One participant was excluded from the analysis because EEG data were not collected for all conditions due to a technical failure.

3. Randomization and blinding

Participants were randomized in a 1:1 allocation to one of two treatment sequences (10 kHz→Burst or Burst→ 10 kHz) using sequentially numbered randomization envelopes opened by the study research nurse post implant. Participants were blinded to the stimulation paradigm. Outcome assessments at follow-up visits were performed by a blinded observer. Programming and reprogramming were conducted by an unblinded study nurse who did not perform the blinded assessments. No formal blinding validation procedure was performed (eg, participants were not asked to guess which waveform they had received at the end of each treatment period).

SCS Trial Implantation and Stimulation Paradigms

1. Lead placement and externalization

SCS trial leads were implanted as a day-case procedure following standard care pathways. All participants were implanted with a St. Jude electrode using paraesthesia mapping. If the lead position was suitable for both paradigms, a single electrode was used; if unsuitable for 10 kHz stimulation, a second electrode was placed at the recommended anatomic position (thoracic T9/10-disc level) to enable 10 kHz implantation. Leads were externalized and secured to the skin, then connected to an external implantable pulse generator (IPG) system for the duration of the trial.

Stimulation Conditions

Following two stimulation paradigms were evaluated:

- High frequency: 10,000 Hz stimulation.
- Burst: Five spikes at 500 Hz delivered at 40 Hz (40 bursts/s), at subthreshold amplitude with fixed pulse width (per local standard programming for this waveform).

Crossover Schedule and Washout

After implantation and randomization, participants completed two active stimulation periods of approximately seven to ten days each, in randomized order:

- Sequence A: 10 kHz for seven to ten days → washout until pain returned to ~80% of baseline → Burst for seven to ten days.

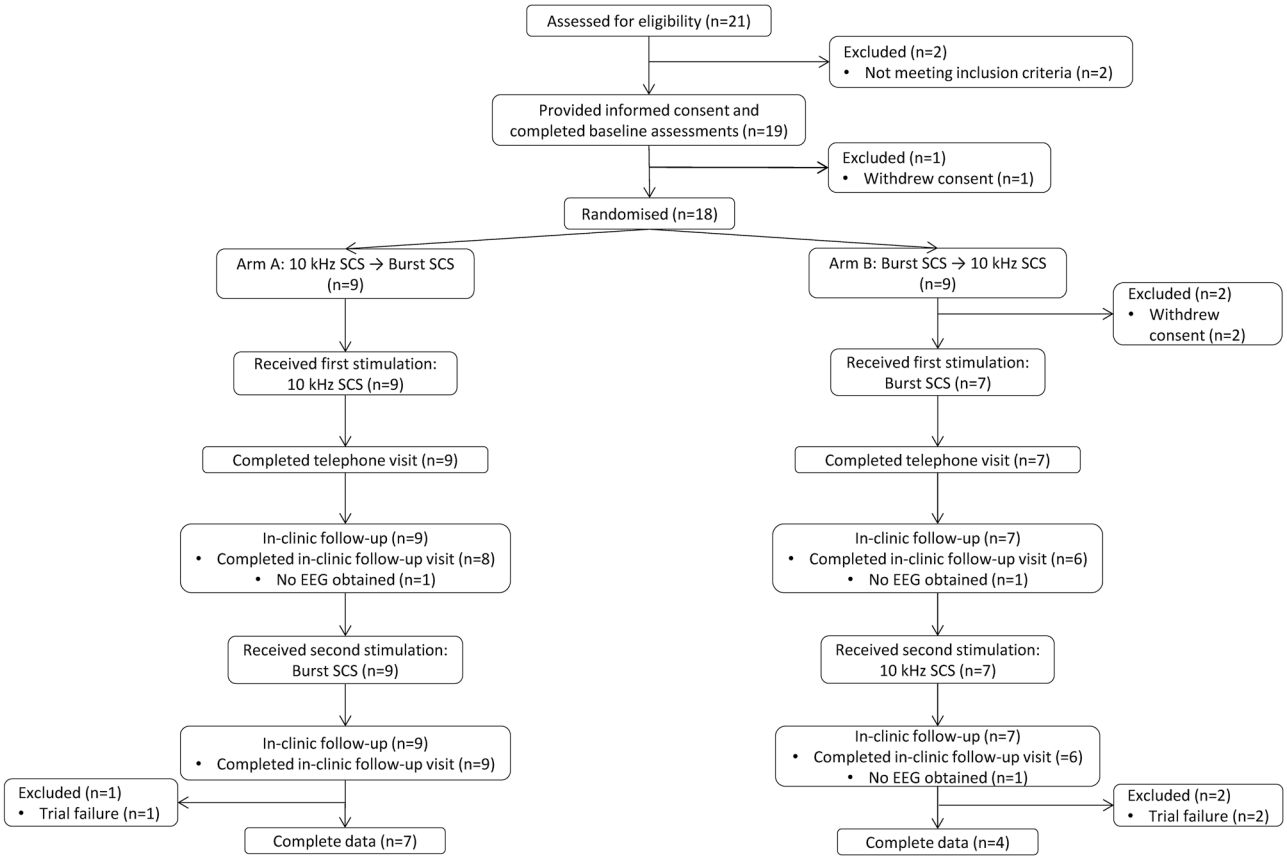

Figure 1. Flowchart.

- Sequence B: Burst for seven to ten days → washout until pain returned to ~80% of baseline → 10 kHz for seven to ten days.

The washout period ranged between 24 and 48 hours maximum.

Washout was defined clinically, not electrophysiologically: participants were instructed to begin the second stimulation period only after pain had returned to approximately 80% of baseline within 24–48 hours. A second EEG baseline was not acquired after washout and before the second treatment period; therefore, return to the original pretreatment cortical state was not directly verified.

At crossover, EEG recorded, reprogramming was completed by the unblinded nurse, and participants were instructed to activate the new settings only after pain returned to ~80% of baseline to reduce carryover effects.

Study Visits and Procedures

- Visit 1 (Baseline): Demographics, vitals, pain history, and relevant medical history; pregnancy exclusion as clinically indicated; completion of questionnaires (VAS back and leg pain); baseline EEG recording.
- Visit 2 (Implant): Trial lead placement and externalization; randomization; programming according to allocation.
- Visit 3 (Telephone, Day 5): Safety and device check, including elicitation of adverse events.
- Visit 4 (End of first period, Day 7–10): Blinded assessment of outcomes and EEG acquisition; reprogramming to alternate paradigm by unblinded nurse; washout instruction.
- Visit 5 (End of second period, Day 7–10): Blinded assessment of outcomes and EEG acquisition; trial lead removal and study exit.

Outcomes

The primary end point was the difference (or similarity) in brain activation patterns between 10 kHz and burst conditions as assessed by EEG recordings obtained at baseline and after each stimulation period.

EEG Processing

1. EEG acquisition and handling

EEG data were collected in a fully lit room with participants seated upright in a small, comfortable chair. Each recording block lasted ~five minutes. Signals were acquired using Mitsar-201 amplifiers (NovaTech; http://www.novatecheeg.com/) from 19 scalp electrodes positioned according to the international 10–20 system. Electrode impedances were maintained below 5 kΩ. Data were recorded eyes closed at a 500 Hz sampling rate with an online bandpass of 0.15–200 Hz. To avoid contamination by active SCS pulses, the IPG/external battery was switched off before each EEG recording. EEG was then acquired immediately after stimulation cessation, during the period of residual inhibition.

2. Preprocessing and artifact handling

Because EEG was recorded after switching off the IPG, the analyzed epochs did not contain ongoing 10 kHz or BurstDR

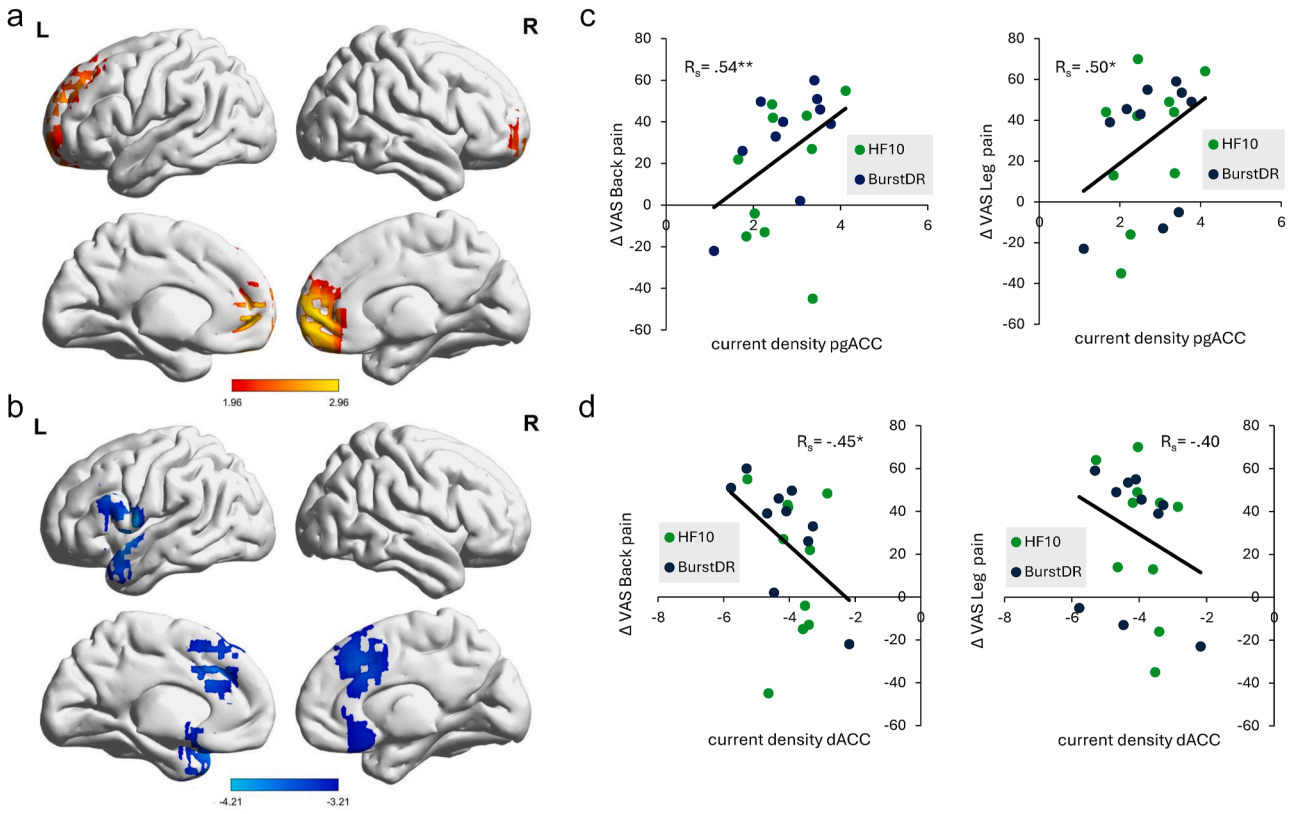

Figure 2. EEG source-level effects of stimulation and associations with pain outcomes. (a) Conjunction analysis (baseline-corrected) showing regions commonly modulated by 10 kHz and BurstDR : Both conditions were associated with increased beta-band activity in the pgACC (b) Baseline-corrected contrast comparing burst vs 10 kHz stimulation revealed reduced alpha-band activity during BurstDR in the dACC, left anterior insula, and subgenual anterior cingulate cortex. (c) Spearman correlation between changes in pgACC beta-band current density from baseline and change in pain from baseline showed significant associations for VAS back and VAS leg. (d) Spearman correlation between changes in dACC current density from baseline and change in pain from baseline showed a significant negative association for VAS back, but not for VAS leg. [Color figure can be viewed at www.neuromodulationjournal.org]

pulses. Preprocessing therefore focused on standard EEG artifact handling rather than removal of continuous stimulation noise. Offline, EEG data were down-sampled to 128 Hz, band-pass filtered (2–44 Hz), imported into Eureka! visually inspected, and cleaned of episodic artifacts (eg, eye blinks and movements, jaw clenching, body movement, and ECG contamination) through careful manual rejection.

Average Fourier cross-spectral matrices were then computed for the following frequency bands: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30.5–44 Hz).

3. Source localization (sLORETA)

Intracerebral electric sources were estimated using sLORETA.[12] Before source analysis, data were transformed to a common average reference[12]. sLORETA estimates neuronal activity as current density (A/m^2) without specifying a predefined number of sources. Source modelling used the solution space and lead field implemented in LORETA-Key (http://www.uzh.ch/keyinst/loreta.htm), incorporating updated realistic electrode coordinates and a boundary element method lead field computed on the MNI-152 template. The LORETA-Key anatomic atlas partitions the neocortical MNI-152 volume (including hippocampus and anterior cingulate cortex) into 6,239 voxels at 5 mm isotropic resolution, on the Demon Atlas,[13] and applies the standard transformation from MNI space to Talairach and Tournoux space.

- EEG montage: 19-channel international 10–20
- Sampling rate: 500 Hz, downsampled to 128 Hz
- Bandpass used for analysis: 2–44 Hz
- Reference for source analysis: common average
- Head model: BEM
- Anatomic template: MNI-152
- Source space: 6,239 voxels
- Voxel size: 5 mm isotropic
- Atlas/parcellation: LORETA-Key atlas / Demon atlas implementation
- Frequency bands: delta, theta, alpha, beta, gamma
- Recording timing: after IPG switch-off during residual inhibition

4. Region-of-interest analysis

For the region-of-interest analyses, we extracted mean current density from anatomically defined volumes of interest (VOIs) in the alpha band for the dorsal anterior cingulate cortex (dACC) and in the beta band for pregenual anterior cingulate cortex (pgACC), rather than using a single voxel to represent each region. This approach was adopted to reduce susceptibility to noise and to avoid voxel-selection

bias. Region of interest (ROI) values represent the transformed proportion of total whole-brain power attributable to each anatomically defined VOI for the specified frequency band.

EEG was acquired with a conventional 19-channel 10–20 montage, which is compatible with the normative data set used by the analysis pipeline but provides limited spatial precision for source localization. Accordingly, anatomic attribution of sLORETA peaks—particularly for closely adjacent midline regions, such as pgACC vs dACC, and for deeper structures, such as the insula—should be regarded as exploratory.

Safety Monitoring and Adverse Event Reporting

At each participant contact, adverse events (AEs) were actively elicited by questioning and assessment as appropriate, recorded in source documents and AE forms, and graded by severity (mild/moderate/severe) and duration (single/intermittent/persistent). The relationship to the procedure/device was adjudicated by the investigator. Serious adverse events (SAEs) were reported to the Sponsor within 24 hours of becoming aware, with reporting timelines aligned with regulatory and ethics requirements. The AE reporting window spanned study entry through 30 days after study completion or withdrawal.

Ethics, Confidentiality, and Oversight

The study was conducted in accordance with ICH-GCP and the Declaration of Helsinki and received ethical approval before initiation. Confidentiality was maintained using study identifiers; access to identifiable data was restricted to appropriate clinical/research oversight functions. Monitoring and audits were permitted in accordance with sponsor and regulatory requirements.

Statistical Analysis

This study was designed as an exploratory pilot crossover study. A formal a priori sample size calculation for the primary EEG end point was not performed because reliable variance estimates for within-subject sLORETA current-density changes under 10 kHz and BurstDR in this patient population were not available at the time of study design. The sample size was therefore on the basis of the feasibility and on the aim of generating preliminary effect-size and variance estimates for a future adequately powered confirmatory study.

1. Pain outcomes

VAS pain scores at baseline, during high-frequency (10 kHz) stimulation, and during BurstDR were analyzed using a repeated-measures ANOVA (within-subject factor: condition). When the main effect was significant, post hoc pairwise comparisons were performed using Bonferroni correction for multiple testing. A similar analysis was conducted for VAS leg pain. Because the primary analyses were conducted using repeated-measures ANOVA, we reported eta squared (η2\eta-2η2) as the corresponding omnibus effect size.

2. EEG analysis

We used a nonparametric permutation-based randomization approach to derive the empirical null distribution of the maximum statistic (max-statistic)19. This procedure provides family-wise error control by correcting for multiple comparisons across all voxels and frequency bands. Because it is nonparametric, the method does not depend on Gaussian assumptions.[14] Statistical significance for all analyses was determined using 5,000 permutations.

Burst and 10 kHz stimulation were compared by first subtracting the baseline measurement for each condition and then computing the 10 kHz–Burst contrast. 10 kHz and Burst end-of-period EEG recordings were analyzed with reference to the single preimplant baseline recording obtained at Visit one, after which the 10 kHz–Burst contrast was computed. Because a second preperiod baseline EEG was not acquired after washout, these baseline-referenced contrasts cannot fully exclude period or residual carryover effects. Whole-brain differences were assessed using sLORETA statistical contrast maps, on the basis of voxel-wise tests expressed as the logarithm of the F-ratio.

We performed a conjunction analysis of 10 kHz and BurstDR after subtracting baseline activity for each condition. Conjunction analysis is used to identify a shared (common) processing component across two or more conditions by locating regions that are consistently significant across the corresponding independent contrasts.[15–18] By referencing both 10 kHz and burst recordings to the single preimplant baseline, we estimated stimulation-associated changes relative to the initial untreated state. However, because no second baseline EEG was obtained before the crossover period, these contrasts should not be interpreted as definitive within-period baseline-corrected effects for both treatment periods. Whole-brain similarities were assessed using sLORETA statistical maps, on the basis of voxel-wise conjunction expressed by a *Z*-score.

For reference we also include the power density plot for both the comparison between 10 kHz and BurstDR by first subtracting the baseline measurement for each condition as well as the conjunction analysis of 10 kHz and BurstDR after subtracting baseline activity (Supplementary Figure 1).

3. Correlation analysis

Spearman rank correlations were used to examine associations between changes in VOI-averaged current density and changes in pain ratings. Specifically, for each stimulation condition, current density change was defined as poststimulation minus baseline, and pain change was defined as poststimulation minus baseline for VAS back pain and VAS leg pain. We then tested the association between Δ beta-band current density in the pgACC and Δ pain, as well as between Δ alpha-band current density in the dACC and Δ pain.

RESULT

Pain Outcomes

Repeated-measures analyses showed a significant effect of condition for both VAS back pain ($F = 5.08$, $p = 0.033$, $\eta^2 = 0.53$) and VAS leg pain ($F = 4.71$, $p = 0.040$, $\eta^2 = 0.51$) (Table 1). For VAS

Table 1. Mean VAS Scores for Back and Leg pain at Baseline, During High-frequency (10 kHz) Stimulation, and During BurstDR.

	Baseline	10 kHz	Burst	*F-value*	*p-value*
VAS BACK	55.09a	38.96a,b	27.12b	5.08	.033
VAS LEG	61.55a	34.26b	34.82b	4.71	.040

Differences in subscripts indicate a significant difference ($p < 0.05$).

back pain, pairwise comparisons showed a significant reduction from baseline during BurstDR, but not during 10 kHz stimulation (Table 1). However, the direct comparison between 10 kHz and burst was not significant. Therefore, although burst showed a numerically larger reduction in back pain, superiority over 10 kHz cannot be concluded from these data (Table 1). For VAS leg pain, pairwise comparisons showed significant reductions from baseline during both 10 kHz and BurstDR. However, there was no significant difference between 10 kHz and BurstDR for leg pain.

EEG Analysis

A conjunction analysis controlling for baseline showed a significant effect ($Z = 1.96$, $p < 0.05$), indicating that both 10 kHz and burst showed shared beta-band increases with a peak localized to the pregenual anterior cingulate region (Fig. 2a). No effect was obtained for the delta, theta, alpha, and gamma frequency bands.

A direct comparison between 10 kHz and BurstDR, controlling for baseline, showed a significant effect ($F = -3.21$, $p < 0.05$, $\eta^2 = 0.24$). Relative to 10 kHz stimulation, burst was associated with reduced alpha-band activity in a medial frontal/anterior cingulate–operculo-insular pattern, with sLORETA maxima assigned by the atlas to the dACC, sgACC, and left anterior insular region. Given the 19-channel montage, these anatomic assignments should be interpreted cautiously (Fig. 2b). No effect was obtained for the delta, theta, beta, and gamma frequency bands.

Correlation Analysis

A Spearman correlation showed that change in beta-band current density from baseline in the pgACC was significantly associated with changes in pain from baseline for both VAS back (Rs = 0.51, $p = 0.023$) and VAS leg (Rs = 0.64, $p = 0.002$). The positive correlations indicate that higher changes in pgACC current density were associated with greater pain reduction in both the back and leg, or vice versa (Fig. 2c).

A similar Spearman correlation analysis examined the association between changes dACC current density from baseline and changes in pain from baseline. Changes dACC current density was negatively correlated with changes in VAS back pain (Rs = −0.51, $p = 0.022$), indicating a significant association, but not with VAS leg pain (Rs = −0.51, $p = 0.023$), which did not reach significance. The negative correlation for back pain suggests that lower dACC activity was associated with greater reductions in back pain (Fig. 2d).

DISCUSSION

The aim of within-subject pilot study was to explore shared and differential clinical and cortical network effects associated with two paraesthesia-free SCS paradigms, 10 kHz and burst, in the same patients. Clinically, 10 kHz and burst produced comparable reduction of leg pain. For back pain, burst showed a statistically significant and clinically pain reduction from baseline, whereas 10 kHz showed a clinically relevant but not statistically significant reduction. Although the magnitude of back pain reduction was numerically larger for burst (–28) than 10 kHz (–16), the between-condition comparison was not statistically significant in this pilot sample. This likely reflects the limited power and interindividual variability.

At the neurophysiologic level, both stimulation paradigms were associated with shared activation within the pgACC, whereas burst was associated with additional changes involving ACC subregions and the insula.

Shared pgACC Modulation is Consistent with Engagement of Descending Pain Inhibition

The conjunction analysis showed shared beta activation in the pgACC during both 10 kHz and burst. Importantly, pgACC activation correlated with the degree of pain suppression across stimulation conditions for both back and leg pain. The pgACC has been consistently implicated in endogenous analgesia and top-down modulation of nociceptive processing through descending inhibitory pathways.[8,10,11,19] Therefore, the shared pgACC signature supports the interpretation that both 10 kHz and burst recruit a common supraspinal mechanism involved in descending pain control, providing a neurophysiologic correlate of their comparable analgesic effects on leg pain. This is analogous to what has been shown to be common between tonic and BurstDR[8] and may be unsurprising, given that each pulse in 10 kHz is charge-balanced and that 10 kHz is thus a tonic stimulation design. Although 10 kHz can be formally classified as a tonic stimulation design in the sense that each pulse is charge balanced, its mechanism of action is likely different from traditional low-frequency tonic stimulation. Low-frequency tonic stimulation is thought to activate Abeta fibers through ia the pain gate mechanism,[3] whereas 10 kHz has been proposed to block Abeta fibers.[4] This distinction is supported clinically by the requirement for paraesthesia with low-frequency tonic stimulation, in contrast to the paraesthesia-independent effects of 10 kHz.[5] Consistent with this, prior EEG studies have shown that both traditional low-frequency tonic and high frequency 10 kHz stimulation activate the pgACC, but low-frequency stimulation also activates the somatosensory cortex,[6] an effect not observed in the current study.

Burst Shows Additional Changes in Medial Cingulate/Operculo-Insular Circuitry Relevant to Back Pain

Compared with 10 kHz, burst showed additional alpha-band differences in medial cingulate and operculo-insular regions. Because source localization was performed with a 19-channel montage, these effects should not be interpreted as definitive evidence of precise separation between adjacent ACC subregions or of selective insular targeting. Rather, the data are more appropriately viewed as suggesting broader modulation of medial/salience-affective circuitry. Indeed, these regions are central nodes within networks involved in pain salience, affective appraisal, interoception, autonomic, and especially sympathetic regulation, and cognitive-emotional integration.[10,20–23] Notably, in this study dACC deactivation correlated with burst-related back pain reduction, whereas no significant correlation between dACC activity and pain relief was identified in the 10 kHz condition.

This pattern suggests that burst may engage additional medial and salience-related pain networks relevant to back pain; however, the present clinical data do not show statistical superiority over 10 kHz for back pain. Indeed, traditional tonic stimulation has little pain-suppressing effect, and tonic stimulation works through the pgACC, but not the dACC.[1,4]

Given that low back pain is strongly associated with suffering and disability and is the single greatest cause of burden worldwide,[24] additional engagement of the medial suffering pathway (dACC/sgACC/insula) may be clinically relevant and may contribute to the observed pattern of back pain reduction with burst in this

cohort. It should be stressed that 10 kHz also reduced low back pain in this study, although this was not statistically significant. Consistent with recent studies, both 10 kHz and burst outperform traditional tonic stimulation for treatment of back pain.[6,25]

Mechanistic Implications

The present findings partially support the proposal that 10 kHz and burst are mechanistically related paraesthesia-free paradigms. Both engage a shared pgACC signature that correlates with analgesia, consistent with a common descending modulatory pathway, which has been described as a commonality with tonic stimulation as well.[8] Furthermore, this study shows that the amount of pain suppression, both for leg and back pain, correlates with how much the descending pain-inhibitory system can be mobilized. This is consistent with a previous functional magnetic resonance imaging study showing that, for tonic stimulation, the amount of pain suppression also correlated with the amount of pgACC BOLD activation.[26]

However, the additional modulation of dACC, sgACC ,and insula during burst, and the stimulation-specific correlation between dACC deactivation and back pain reduction, argues against complete mechanistic equivalence. Instead, the results are more consistent with a model in which 10 kHz and burst share a core supraspinal mechanism related to descending modulation, while burst may additionally influence medial/salience-affective circuitry. Given the use of a 19-channel EEG montage, the precise anatomical assignment of these effects remains tentative, and these mechanistic interpretations should be regarded as provisional pending confirmation in higher-resolution or multimodal studies.[8]

Translational Relevance

Identification of shared and stimulation-specific cortical signatures provides a preliminary framework for future investigation of biomarker-informed waveform selection. pgACC activation may represent a general marker of tonic (traditional or 10 kHz) SCS engagement and response, whereas dACC/sgACC/insula modulation may differentiate mechanisms relevant to back pain improvement with burst. Future work with larger cohorts and longer duration is warranted to assess whether baseline network features or early EEG signatures can predict preferential response to specific spinal cord stimulation paradigms. Ideally, all available stimulation designs should be compared to select the optimal stimulation design for the individual patient based on biomarker data.

Limitations

This study has limitations. The sample size was modest, and no formal a priori power calculation on the basis of EEG current-density variance was available, reflecting the pilot nature of the study. Accordingly, the findings should be interpreted as exploratory and hypothesis-generating. The present data can, however, inform variance-based sample size estimation for future definitive crossover studies using source-localized EEG current density as the primary end point.

Stimulation periods were limited to approximately ten days per paradigm, and longer-term effects as well as carryover cannot be excluded. Only two previous studies have compared burst and 10 kHz SCS. In a randomized crossover study, patients tended to prefer the first stimulation paradigm administered, and the second stimulation period was consistently less effective.[1] This was coupled with no statistically significant differences in the amount of pain reductions between each stimulation design. This finding was hypothesized to reflect a carry-over effect despite a washout period similar in duration to that used here (24–48 hours).[1] In the second study, patients were not their own controls, and therefore carryover effects could not be assessed.[2]

In the present study, washout was defined clinically by return of pain to approximately 80% of baseline within 24–48 hours, and pain did not necessarily return fully to baseline before crossover. Moreover, only a single baseline EEG was acquired before the first treatment period, and no second preperiod EEG (Baseline 2) was recorded after washout. We therefore cannot confirm neurophysiologically that cortical activity had returned to the original pretreatment state before the second stimulation period, and period or residual carryover effects remain possible. Although randomization of stimulation order mitigates systematic bias, these design features limit causal inference. Accordingly, the EEG findings should be interpreted as hypothesis-generating, representing baseline-referenced between-condition differences rather than definitive within-period effects. Importantly, EEG was not recorded during active stimulation delivery; recordings were obtained immediately after IPG switch-off during residual inhibition and therefore present findings reflect poststimulation brain activity rather than online stimulation artifact.

An important limitation is the use of a conventional 19-channel EEG montage for source localization. Although sLORETA permits exploratory estimation of cortical current-density patterns, low-density EEG provides limited spatial precision, especially when attempting to distinguish closely adjacent regions such as the pregenual and dorsal anterior cingulate cortex, or when inferring activity in deeper structures such as the insula. Accordingly, the regional assignments reported here should be interpreted as tentative atlas-based localizations rather than definitive proof of subregional specificity. In particular, the present data do not establish that burst selectively targets the insula, whereas 10 kHz does not. Confirmation of these regional interpretations will require higher-density EEG, individualized forward models, and/or multimodal imaging, such as concurrent fMRI.

Finally, placebo and expectancy effects cannot be fully controlled without sham stimulation. Although both 10 kHz and burst are paresthesia-free and the study was designed to be double-blind, we did not perform a formal blinding validation (eg, asking participants to guess the waveform received during each treatment period). We therefore cannot empirically confirm the success of blinding. Because resting-state EEG and sLORETA-derived source estimates may be influenced by attentional and emotional state, nonspecific expectancy-related effects cannot be fully disentangled from waveform-specific neurophysiological effects. Accordingly, these findings should be interpreted cautiously. The patients were randomized to start either with burst or 10 kHz which prevents an order effect from explaining the observed outcomes.

CONCLUSION

Burst and 10 kHz were associated shared source-localized EEG changes consistent with engagement of common pain-modulatory circuitry. Burst was additionally associated with differences within broader medial cingulate/operculo-insular regions, however the spatial precision of the 19-channel sLORETA approach does not permit definitive subregional localization. These findings should

therefore be considered exploratory and hypothesis-generating. Overall, these results support partial mechanistic overlap between paraesthesia-free paradigms, alongside waveform-specific network modulation that may be clinically relevant, particularly for axial back pain.

Authorship Statements

Dirk De Ridder contributed to methodology and writing. Ganesan Baranidharna contributed to methodology, writing, and data collection. Beatrice Bretherton contributed to writing and data collection. John Titterington, Sheila Black, Tracey Crowther, and Sangeetha Das contributed to writing and data collection, and Sven Vanneste contributed to writing and data analysis. All authors approved the final version of the manuscript. Given their role as a *Neuromodulation* Editorial Board member, Dirk De Ridder was not involved in the peer-review of this article and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Conflict of Interest

Ganesan Baranidharan reports consulting income from Boston Scientific, Globus Medical, Saluda Medical, Mainstay Medical, Artha Medical and stock or stock options from Nalu Medical. Dirk De Ridder reports consulting income from Abbott. He has an IP on BurstDR™ but has no financial benefit from sales. Beatrice Bretherton reports consulting income from Abbott. None of the other authors has any conflict of interest related to the research conducted.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2026.05.014.

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COMMENT

This paper is a very neat and clever way to harvest data that allows us to peer inside what SCS waveforms are doing to the patient. We have made great strides understanding the activation and propagation of spinal cord signals but by the time it passes through the brainstem, things start to get quite uncertain and murky—because of varying pain signatures, varying brain signatures and the lack of the most extreme fidelity in spatial resolution to know what is being stimulated/inhibited where. This paper gives us a glimpse into this subject and more importantly than the results, it shows us that it is possible and could likely become part of the trial/early implant armamentarium to guide or optimise therapy.

The results, hypothesis generating as they are rather than definitive, certainly do not disprove the theoretical rationale that burst waveforms

modulate more than one aspect of the pain experience. I can see we need more work here and that it will be a very fruitful area of optimisation. We simply cannot spend all our time optimising the cord then in the brain "things are the way they are" and we think that all parameters have been fine tuned. There is the possibility of just as much, if not more, fine tuning that we could do in the brain if we can measure it accurately enough. As I have mentioned before, could we ever have one optimised signal for the cord and yet another for the brain? Food for thought.

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