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Pulse Intensity Effects of Burst and Tonic Spinal Cord Stimulation on Neural Responses to Brushing in Patients With Neuropathic Pain

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ABSTRACT

Objectives: Tonic spinal cord stimulation (SCS) is accompanied by paresthesia in affected body regions. Comparatively, the absence of paresthesia with burst SCS suggests different involvement of the dorsal column system conveying afferent impulses from low-threshold mechanoreceptors. This study evaluated cortical activation changes during gentle brushing of a pain-free leg during four SCS pulse intensities to assess the effect of intensity on recruitment of dorsal column system fibers during burst and tonic SCS.

Materials and Methods: Twenty patients using SCS (11 burst, nine tonic) for neuropathic leg pain participated. Brushing was administered to a pain-free area of the leg during four SCS intensities: therapeutic (100%), medium (66%), low (33%), and no stimulation. Whole-brain electroencephalography was continuously recorded. Changes in spectral power during brushing were evaluated using the event-related desynchronization (ERD) method in theta (4–7 Hz), alpha (8–13 Hz), and beta (16–24 Hz) frequency bands.

Results: Brushing was accompanied by a suppression of cortical oscillations in the range 4–24 Hz. Stronger intensities of burst and tonic SCS led to less suppression of 4–7 Hz and 8–13 Hz bands in parietal electrodes, and in central electrodes in the 16–24 Hz band, with the strongest, statistically significant suppression at medium intensity. Tonic SCS showed a stronger reduction in 4–7 Hz oscillations over right sensorimotor electrodes, and over right frontal and left sensorimotor electrodes in the 8–13 Hz band, compared to burst SCS.

Conclusions: Results suggest that burst and tonic SCS are mediated by both different and shared mechanisms. Attenuated brushing-related ERD with tonic SCS suggests a gating of cortical activation by afferent impulses in the dorsal column, whereas burst may engage different pathways. Diminished brushing-related ERD at medium and therapeutic intensities of burst and tonic SCS points towards a nonlinear effect of SCS on somatosensory processing.

Keywords: Electroencephalography, humans, neuropathic pain, spinal cord stimulation, time-frequency

Conflict of Interest: Danielle Hewitt has received studentship funding from Abbott. The remaining authors reported no conflict of interest.

INTRODUCTION

Spinal cord stimulation (SCS) is a cost-effective[1] analgesic neurostimulation method for the relief of neuropathic pain.[2–4] However, only 62% of patients who undergo permanent SCS implantation experience adequate pain relief,[5] and an estimated 30% of all implanted devices are removed.[6] A lack of effectiveness could be, in part, due to our limited understanding of the therapeutic mechanisms of SCS.[7]

SCS was developed as a direct application of the gate control theory,[8] whereby antidromic activation of Aβ fibers in the dorsal column closes a spinal "gate" to inhibit the transmission of nociceptive input, and orthodromic activation of Aβ fibers results in paresthesia in the painful area.[8–11] Accordingly, the literature suggests that tonic SCS works by gating the transmission of noxious stimuli.[12,13] In contrast, more recent stimulation patterns such as burst[14] are suggested to have different mechanisms of action.[15–18] Burst SCS utilized in the current study consists of trains of five

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monophasic pulses administered at 40 Hz interburst and 500 Hz intraburst frequencies, which are charge balanced after each pulse train.[14,17,19] As burst SCS is set below perceptual threshold, it does not produce paresthesia and may not activate dorsal column Aβ afferents.[20] In vivo studies have indicated that, in contrast to tonic SCS, burst SCS does not act through spinal gamma-aminobutyric acid (GABA)-ergic mechanisms;[21] however, a more recent study showed that GABAergic modulation may be involved during active-recharge burst programs.[22] Therefore, mixed evidence suggests that the spinal mediators of burst SCS differ from tonic stimulation.

The intensity of SCS may interact with its effect on somatosensory processing. Stimulation intensity or amplitude influences the number of fibers recruited by stimulation and is one of many parameters that determine electrical charge transfer.[23] Electrical charge transfer is a critical factor in SCS effectiveness; increased intensity is associated with reduced neuronal firing to noxious stimuli and nonlinear increases in wide dynamic cell responsiveness with burst SCS,[24] and a greater reversal of nociceptive behaviors in animal studies with tonic SCS.[25,26] However, the effect of stimulus intensity on somatosensory processing during burst SCS has yet to be investigated.

Electroencephalography (EEG) can be used to investigate changes in ongoing neural activity. Sensory stimuli can induce decreases or increases of power in given frequency bands, phenomena known as event-related desynchronization (ERD)[27,28] and event-related synchronization (ERS),[29] respectively. ERD and ERS are respectively related to states of activation[27,28] and inhibition[30,31] within the sensorimotor system. Tactile brushing stimuli are associated with alpha- and beta-band ERD over bilateral primary sensorimotor cortices at a latency of 250 to 400 milliseconds after stimulus onset, followed by 20 Hz ERS over the precentral cortex at 450 to 700 milliseconds.[32–34] Somatosensory brushing stimuli administered at slow velocities of 3 cm per second are also associated with slow-wave 6 Hz oscillations at 1 to 3 seconds after stimulus onset over frontal areas of the scalp.[35] The effects of SCS on ERD have yet to be investigated; however, tonic SCS has been shown to inhibit somatosensory processing of innocuous nerve stimulation.[36–42] Increased resting-state cortical oscillations have been reported in patients with chronic pain in theta (4–7 Hz), alpha (8–13 Hz), beta (16–30 Hz), and delta (1–4 Hz) frequency bands relative to healthy controls.[43] Alterations in alpha- and beta-band power have been observed between different SCS waveforms, leading to the suggestion that burst SCS modulates affective, motivational aspects of pain through engagement of the medial pain pathway.[17,44] Likewise, burst SCS has been shown to increase activation in regions including the raphe nucleus, nucleus accumbens, caudate putamen,[45] and anterior and posterior cingulate cortex.[46] These findings suggest that alterations in neural oscillatory power may have clinical relevance for the treatment of chronic pain with SCS.

This study sought to investigate the effects of burst and tonic SCS on somatosensory ERD evoked during brushing of the leg in theta (4–7 Hz), alpha (8–13 Hz), and beta (16–24 Hz) frequency bands. Secondly, the study investigated the effect of SCS intensity on ERD during brushing at four intensities: low, medium, therapeutic, and off. We predicted that somatosensory ERD in alpha and beta frequency bands would be present during brushing when SCS was switched off, and ERD would decrease when SCS was switched on and with increasing stimulation intensity. Due to the previous evidence of differences between SCS types, with burst SCS predominantly engaging the medial pain system,[44,46] we hypothesized that differences between tonic and burst SCS in brushing-related ERD would be found in frontal and midline regions.

MATERIALS AND METHODS

Subjects

Twenty-one patients with unilateral (17) or bilateral (4) neuropathic lower limb pain were recruited from The Walton Centre National Health Service (NHS) Foundation Trust, Liverpool, UK. All participants had previously undergone implantation with Abbott SCS devices (Abbott, TX) in tonic ($N = 10$) or BurstDR™ waveforms ($N = 11$). One subject was excluded due to incomplete data. The final sample included 20 participants (11 women) with a mean age of 52.5 ± 12.3 years (mean ± SD). The procedure used was approved by the Liverpool Central North West Research Ethics Committee, and all participants gave fully informed written consent at the start of the experiment, in accordance with the Declaration of Helsinki. Participants were reimbursed with £40 for their time on completion of the study.

Patient characteristics are summarized in Table 1. Mean duration of SCS implant was 16.6 months, and mean duration of symptoms was 126.35 months. A one-way analysis of variance (ANOVA) showed no significant difference of symptom duration ($F(1,19) = 2.32$, $p > 0.05$), SCS duration ($F(1,19) = 0.54$, $p > 0.05$), age ($F(1,19) = 0.14$, $p > 0.05$), or sex ($F(1,19) = 0.69$, $p > 0.05$) between patients using burst and tonic SCS. Target stimulation amplitude was available for ten patients and ranged from 0.2 to 6.3 mA. Analgesic medications were not withdrawn before participating; 15 patients were using pain medication, with 13 patients using two or more pain medications.

Experimental Protocol

Experimental procedures were carried out in a single two-hour session in the Research Laboratory, Pain Research Institute, Aintree University Hospital NHS Foundation Trust (Liverpool, UK). Participants' SCS devices were turned off for approximately 40 minutes from the time of arrival while EEG electrodes were applied.

During the experiment, participants were seated in a comfortable armchair with legs raised at a 45° angle. The experiment consisted of four blocks, consisting of 40 cycles of 4 seconds of mechanical brush stimulation followed by 4 seconds of rest. The experimenter manually applied brush strokes to a pain-free area of the participant's leg (Table 1) using a synthetic soft-bristled paintbrush with bristles measuring 4 cm × 6.5 cm × 2 cm. In 18 of 20 patients, brush strokes consisted of one continuous motion for 10 cm along the tibialis anterior muscle, starting at one-third of the distance between the patella and the lateral malleolus and then returning to the starting point at a rate of 5 cm per second for 4 seconds. In two patients who reported pain and/or numbness in this region, brushing was delivered for 10 cm along the vastus lateralis muscle above the knee at the same rate. At the start and end of each block were 30 seconds of no stimuli. Brushing was controlled using a metronome audio clip played to the experimenter through noise-canceling headphones, which corresponded to EEG stimulus onset and offset triggers.

Blocks were varied by SCS intensity determined using the patient programmer: therapeutic intensity, medium (66% of the therapeutic level), low (33% of the therapeutic level), and no stimulation. Therapeutic intensity was defined as the typical intensity used by each patient, determined as part of their normal clinical care. Block order was varied pseudorandomly for each participant. SCS was turned off for 2 minutes between blocks. During this time, the participants were asked to rate the intensity and uncomfortableness of the brushing stimuli on a numeric rating scale, from no

Table 1. Clinical Patient Characteristics.

ID	Age (y)	Sex	Diagnosis	Pain duration	Brush area	SCS type	SCS duration	Lead	Lead location	IPG	Freq (Hz)
1	63	F	Neuropathic radicular right leg pain	228	Left lower leg	Burst	30	Octrode	T10–T12	Prodigy	40
2	46	F	Neuropathic right leg pain secondary to MS	108	Left lower leg	Burst	29	Lamitrode Tripole	T10–T12	Prodigy	40
3	68	F	Bilateral neuropathic leg secondary to MS	168	Left lower leg	Burst	48	Octrode x2	T9–T11	Prodigy	40
4	59	M	Neuropathic radicular left leg pain	48	Right upper leg	Tonic	2	Lamitrode Tripole	T9–T10	Prodigy	40
5	53	M	Bilateral lower limb neuropathic pain	267	Right lower leg	Tonic	2	Lamitrode Tripole	T9–T10	Prodigy MRI	40
6	52	M	Bilateral neuropathic leg pain secondary to MS	60	Left upper leg	Burst	30	Lamitrode Tripole	T10–T12	Prodigy	40
7	61	F	Neuropathic bilateral leg pain	84	Right lower leg	Tonic	1	Octrode	T9–T12	Prodigy	30
8	50	F	Right foot CRPS	46	Left lower leg	Tonic	25	Octrode x2	T9–T11	Prodigy	50
9	76	M	Neuropathic right foot pain	96	Left lower leg	Tonic	36	Lamitrode Tripole	T12–L1	Prodigy	60
10	50	M	Neuropathic radicular left leg pain	84	Right lower leg	Burst	1	Octrode	T9–T11	Prodigy	40
11	39	M	Neuropathic left foot and ankle pain	84	Right lower leg	Burst	1	Octrode x2	T8–T11	Prodigy	40
12	37	F	Neuropathic radicular left leg pain	60	Right lower leg	Tonic	16	Octrode x2	T8–T11	Prodigy	50
13	30	F	Neuropathic radicular left leg pain	72	Right lower leg	Tonic	1	Lamitrode Tripole	T8–T9	Prodigy	40
14	55	F	Neuropathic left foot and ankle pain	240	Right lower leg	Burst	24	Octrode	T10–T12	Prodigy	40
15	75	F	Neuropathic radicular left leg pain	420	Right lower leg	Burst	8	Octrode x2	T8–T12	Prodigy	40
16	52	M	Neuropathic radicular left leg pain	192	Right lower leg	Burst	12	Lamitrode Tripole	T9–T10	Prodigy	40
17	52	F	Neuropathic radicular left leg pain	60	Right lower leg	Burst	12	Octrode x2	T9–T12	Prodigy	40
18	52	F	Neuropathic radicular left leg pain	48	Right lower leg	Tonic	12	Octrode x2	T8–T10	Prodigy	44
19	36	F	Left foot and ankle CRPS-II	66	Right lower leg	Burst	12	Octrode	T10–T12	Prodigy	40
20	44	M	Neuropathic radicular right leg pain	96	Left lower leg	Tonic	19	Octrode	T10–T12	Prodigy	50

Pain duration and SCS duration measured in months.
CRPS, complex regional pain syndrome; F, female; Freq, frequency in hertz (Hz); ID, identifier; IPG, implantable pulse generator; M, male; MS, multiple sclerosis.

(0) to maximum sensation (100), and whether the brushing was painful. The experiment lasted approximately 25 minutes.

Age, duration of pain, and duration of SCS treatment were collected verbally from patients. Patients self-completed the Neuropathy Pain Scale by hand or tablet. Pain diaries were collected for seven days after the visit to assess average and strongest pain scores using a numeric rating scale from no pain (0) to worst imaginable pain (10). Patient diagnosis and SCS parameters were confirmed by a clinician (Dr Bernhard Frank).

EEG Acquisition

Whole-scalp EEG was continuously recorded using a 63-channel system (BrainProducts GmbH, Munich, Germany). Actively shielding Ag-AgCl electrodes were mounted on an electrode cap (actiCap snap, BrainProducts GmbH) according to the International 10–20 system.[47] The cap was aligned with respect to anatomical landmarks of two preauricular points, the inion and the nasion. Electrolyte gel was applied to achieve electrode-to-skin impedances < 50 kΩ throughout the experiment. A recording band-pass filter was set at 0.001 to 200 Hz, with a sampling rate of 1000 Hz. Electrode Fz was used as a reference electrode, and electrode FPz was used as the ground electrode. EEG average reference was applied, and signals were digitized at 1 kHz with a BrainAmp DC amplifier (actiChamp), connected to BrainVision Recorder 2.0 running on a Windows 10 laptop.

Spectral Analysis of EEG Signals

EEG data were processed in MATLAB (MathWorks, Natick, MA) using the EEGLab toolbox.[48] Continuous EEG data during brushing were split into 8-second epochs. Data were rereferenced to the common average[49] and filtered from 1 to 100 Hz. Data were visually inspected for movement and muscle artifacts. Epochs containing motion, electrode, or muscle artifacts were excluded from further analysis. Electrode channels with large artifacts were interpolated to a maximum of 10% of all electrodes. The average number of epochs remaining after artifact correction for each condition were: no stimulation 33 ± 4, low intensity 34 ± 3, medium intensity 34 ± 3, and therapeutic intensity 34 ± 4. Accepted trials were not significantly different between SCS intensity conditions ($F(3,54) = 0.82$, $p = 0.491$) or SCS type ($F(1,18) = 0.09$, $p = 0.771$).

Power spectra were computed in FieldTrip[50] (http://fieldtriptoolbox.org) using a discrete Fourier time-frequency transformation. Power spectral densities were computed using Welch's method in 1-second windows shifted in overlapping 0.1-second segments to yield a power time series of 80 points, representing the interval from −4 to 4 seconds from the onset of brushing. Data were smoothed using a 4 Hz Slepian sequence. Spectral power was estimated in the range of 1 to 100 Hz, with a frequency resolution of 0.977 Hz. Due to SCS stimulation artifacts between 40 and 60 Hz (Table 1), only frequency components between 1 and 30 Hz were considered for statistical analysis. Relative power was evaluated using the classical ERD transformation[51]:

$$D\% = \left(100 * \frac{A-R}{R}\right)$$

where D represents the percentage power change during epochs after the onset of brushing (A) relative to a preceding baseline or reference period (R, −3 to −1 seconds). Positive D values correspond to relative power decreases (ERD).[27,28] Negative D values correspond to increases in EEG band power (ERS).[29]

Statistical Analysis

Behavioral Ratings

Mean subjective intensity and discomfort ratings of brushing stimuli in each condition were calculated for each participant. A 2 × 4 repeated measures ANOVA was computed using SPSS (version 25, IBM, Inc, Armonk, NY), with independent variables of SCS type (tonic or burst SCS) and intensity (no stimulation, low, medium, or therapeutic SCS intensity). Post hoc t-tests were used when appropriate to follow up significant main effects.

ERD Data

Individual and grand-average topographic plots were visually inspected to identify electrodes showing prominent ERD (> 5% power change) during brushing. Grand-average time-frequency plots from electrodes of interest were used to determine frequency bands showing ERD during brushing in the range of 1 to 30 Hz. The peristimulus brushing interval was split into seven 0.5-second time windows from 0 to 3.5 seconds.

To examine the effects of SCS intensity, one-way repeated measures ANOVAs were computed in each frequency band across every electrode and time bin of interest, in patients using both tonic and burst SCS. To control for type I error likely to occur owing to the large number of ANOVAs, the resulting statistical probability values were subject to permutation analysis with 1000 permutations, implemented using the *statcond.m* program in the EEGLab package.[52] Permutation analysis provides a data-driven approach to test effects across all time bins and electrodes of interest whilst controlling for multiple comparisons with no loss in statistical power.[52] Secondly, to avoid spurious results showing only minimal changes in power from baseline, electrodes surpassing permutation tests at a predefined threshold ($p < 0.05$) for the main effect of intensity were entered into univariate t-tests to confirm that band power differed significantly from zero. Electrodes deemed significant in both permutation testing and univariate t-tests were selected for further analysis and clustered based on spatial adjacency. Pairwise comparisons were computed to further investigate significant main effects. The Huynh-Feldt correction was used to tackle violations of sphericity.

The effects of stimulation type (burst vs tonic SCS) at every electrode and time bin were evaluated using unpaired t-tests (corrected probability $p = 0.05$). Statistical probability values were subject to permutation analysis with 1000 permutations. Electrodes showing a significant main effect of SCS type or intensity were entered into mixed-methods ANOVAs to analyze the interaction between conditions.

RESULTS

Behavioral Data

Neuropathic pain symptoms were evaluated using the Neuropathy Pain Scale. A one-way ANOVA showed no significant difference in neuropathic pain scores between burst and tonic SCS (mean = 45.7 ± 18.2; $F(1, 19) = 0.05$, $p > 0.05$). In the seven days after the experiment, pain diaries were collected. Five patients did not complete the diaries. A one-way ANOVA showed no significant difference between mean average (mean = 5.1; $F(1, 13) = 4.3$, $p > 0.05$) and strongest (mean = 6.4; $F(1, 13) = 4.2$, $p > 0.05$) pain ratings in completed diaries between burst and tonic SCS. Two of

20 patients reported pain resulting from brushing stimuli. Repeated measures ANOVA showed no significant difference in mean intensity (31.94 ± 24.07) or discomfort (4.05 ± 11.12) during brushing between SCS type or intensity ($p > 0.05$).

ERD During Brushing

After visual inspection of individual and grand-average topographic plots across all 63 electrodes, a set of 33 electrodes overlying the frontal, central, and parietal regions of the scalp were selected to visualize the time-frequency plots in both SCS types (burst and tonic) and four SCS intensities (no stimulation, low, medium, and therapeutic) during brushing (Fig. 1a). Grand-average time-frequency plots (Fig. 1b) showed band power decreases concentrated between 4 and 24 Hz across all conditions. A qualitative comparison of time-frequency spectra in burst and tonic SCS averaged over all intensities (Fig. 1c,d) showed a similar distribution of ERD in both SCS types, although burst SCS showed decreased power focused around 5 Hz and 13 Hz, whereas tonic SCS showed a more widespread pattern of band-power reduction. Figure 1e–h shows time-frequency plots of EEG signals in each SCS intensity, averaged over burst and tonic SCS types. Visual inspection of time-frequency plots revealed robust ERD in the frequency range of 4 to 24 Hz in all four SCS intensity conditions. To quantify band-power changes in SCS types and intensity, ERD was computed in the frequency bands 4–7 Hz, 8–13 Hz, and 16–24 Hz. ERD curves in the selected frequency bands were divided into seven 0.5-second time bins covering the peristimulation period from 0 to 3.5 seconds.

Effect of SCS Type

The effect of stimulation type in all electrodes and time bins was evaluated using unpaired *t*-tests with a corrected probability value of $p = 0.05$.

In the 4–7 Hz band, greater brushing-related ERD over right sensorimotor and midline electrodes was observed in patients using burst compared to tonic SCS (Fig. 2a). While ERD was weaker in patients using tonic compared to burst SCS across the whole scalp, burst and tonic SCS differed statistically in electrode C4 overlying the right sensorimotor cortical area during the final period of brushing ($t(18) = -2.31$, $p = 0.03$; Fig. 2b–d). This difference was related to a comparatively weak band-power decrease in tonic SCS in the final time bin (3–3.5 seconds).

In the 8–13 Hz band, widespread ERD was observed when the brush touched the leg (Fig. 2e). A significant difference was found in brushing-induced 8–13 Hz band power between burst and tonic SCS during the initial period of brushing (0–0.5 seconds) in right frontal and left parietal electrodes (F4 and P5; Fig. 2f–h, j–k). Both

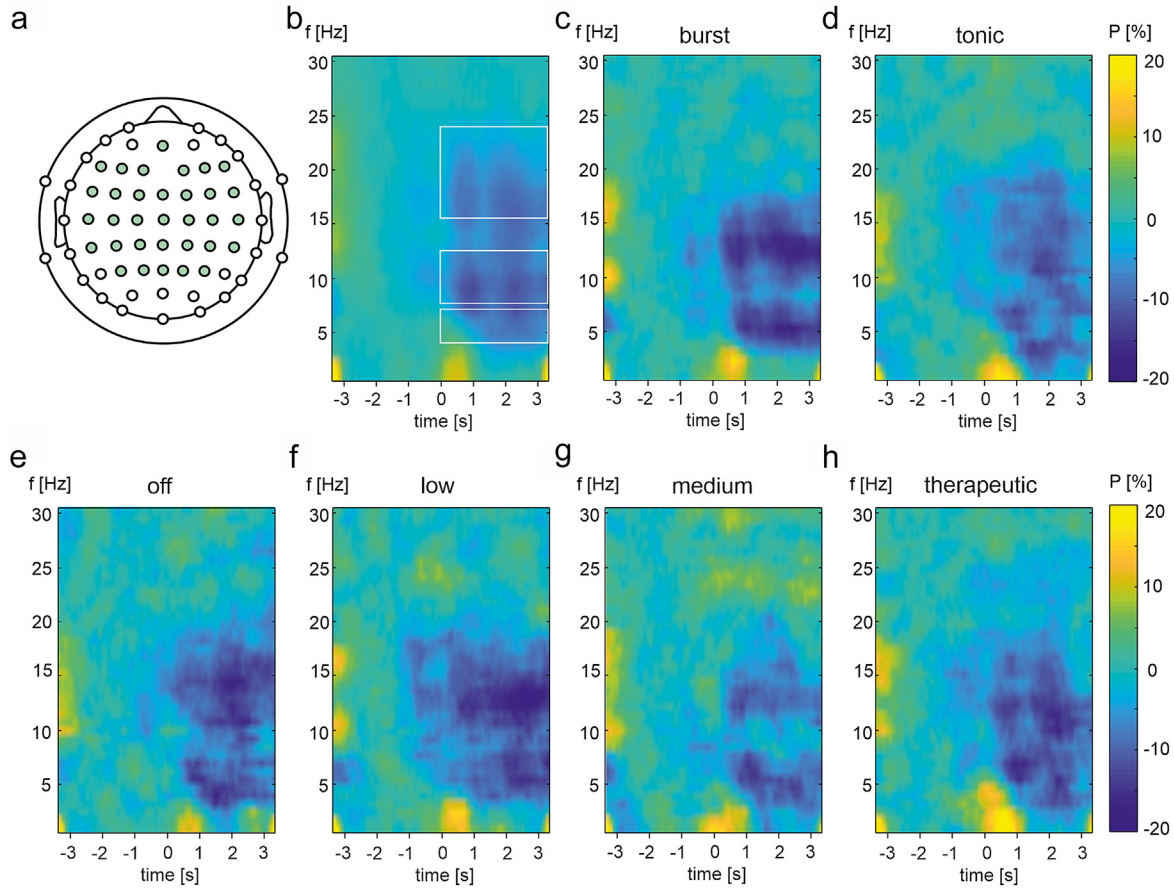

Figure 1. Grand-average ($N = 20$) band-power changes during rest (−3 to 0 seconds) and brushing of a pain-free region of the leg (0–3 seconds). a. An overhead view of electrodes of interest. b. Grand-average time-frequency plots show widespread ERD in frequency bands 4–7 Hz, 8–13 Hz, and 16–24 Hz during brushing. c–h. Time-frequency plots show band-power changes in burst (c) and tonic (d) SCS conditions, averaged over all four intensities, and during SCS off (e), low (f), medium (g), and therapeutic (h) intensity conditions, averaged over SCS type. f, frequency in hertz (Hz); P, percentage power change from baseline. [Color figure can be viewed at www.neuromodulationjournal.org]

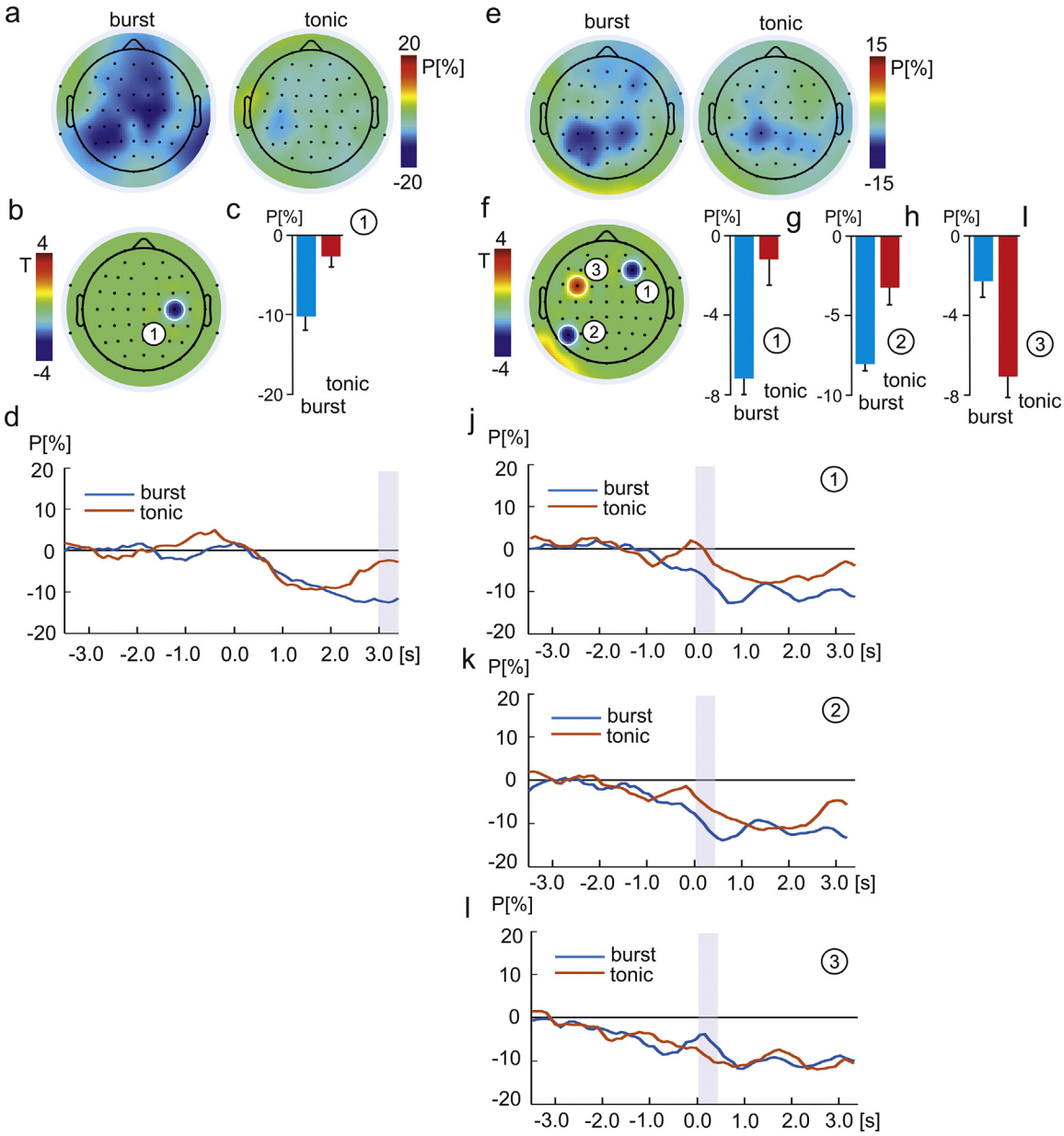

Figure 2. Effect of SCS type on 4–7 Hz and 8–13 Hz oscillatory band power during brushing. Topographic maps show 4–7 Hz (a) and 8–13 Hz (e) band-power changes during burst and tonic SCS, averaged over all SCS intensities in all participants (N = 20). Electrodes and time bins exceeding permutation testing in 4–7 Hz (b) and 8–13 Hz (f) frequency bands were exported for statistical analyses. Bar charts show percentage power change in the corresponding electrode cluster in 4–7 Hz (c) and 8–13 Hz (g–i) frequency bands. Time courses show band-power changes over the duration of brushing for each cluster in 4–7 Hz (d) and 8–13 Hz (j–l) frequency bands, with significant time bins highlighted in gray. Error bars show SE of the mean. [Color figure can be viewed at www.neuromodulationjournal.org]

electrodes showed a comparatively weak band-power decrease in tonic compared with burst SCS (t(18) = −2.62, p = 0.017; t(18) = −2.83, p = 0.011). Comparatively, burst and tonic SCS differed in left frontal-central electrodes (FC3; Fig. 2f), with statistically significant reduced band power in patients using tonic compared with burst SCS (t(18) = −2.34, p = 0.031; Fig. 2i,l).

There was no statistically significant difference in brushing-related ERD in the 16–24 Hz band between burst and tonic SCS.

Due to heterogeneity in the duration of SCS treatment between subjects, univariate analyses of covariance were conducted separately for each of the significant clusters, with SCS treatment duration as a covariate. The covariate effect of SCS treatment duration was not statistically significant in any of the four clusters manifesting a statistically significant difference between burst and tonic SCS (p > 0.05). However, the statistical significance of SCS type in the 4–7 Hz band (F(1,18) = 5.33, p = 0.033) dropped after the inclusion of SCS treatment duration as a covariate (F(1,17) = 4.11, p = 0.059). Likewise, the statistical significance of type of SCS in cluster 3 in the 8–13 Hz band (F(1,18) = 5.49, p = 0.031) decreased after the inclusion of SCS treatment duration as a covariate (F(1,17) = 4.03, p = 0.061). Results suggest that, although the contrast between burst and tonic SCS was not affected by SCS duration in two of the four clusters, SCS duration explained a fraction of the burst-tonic contrast in the two other clusters.

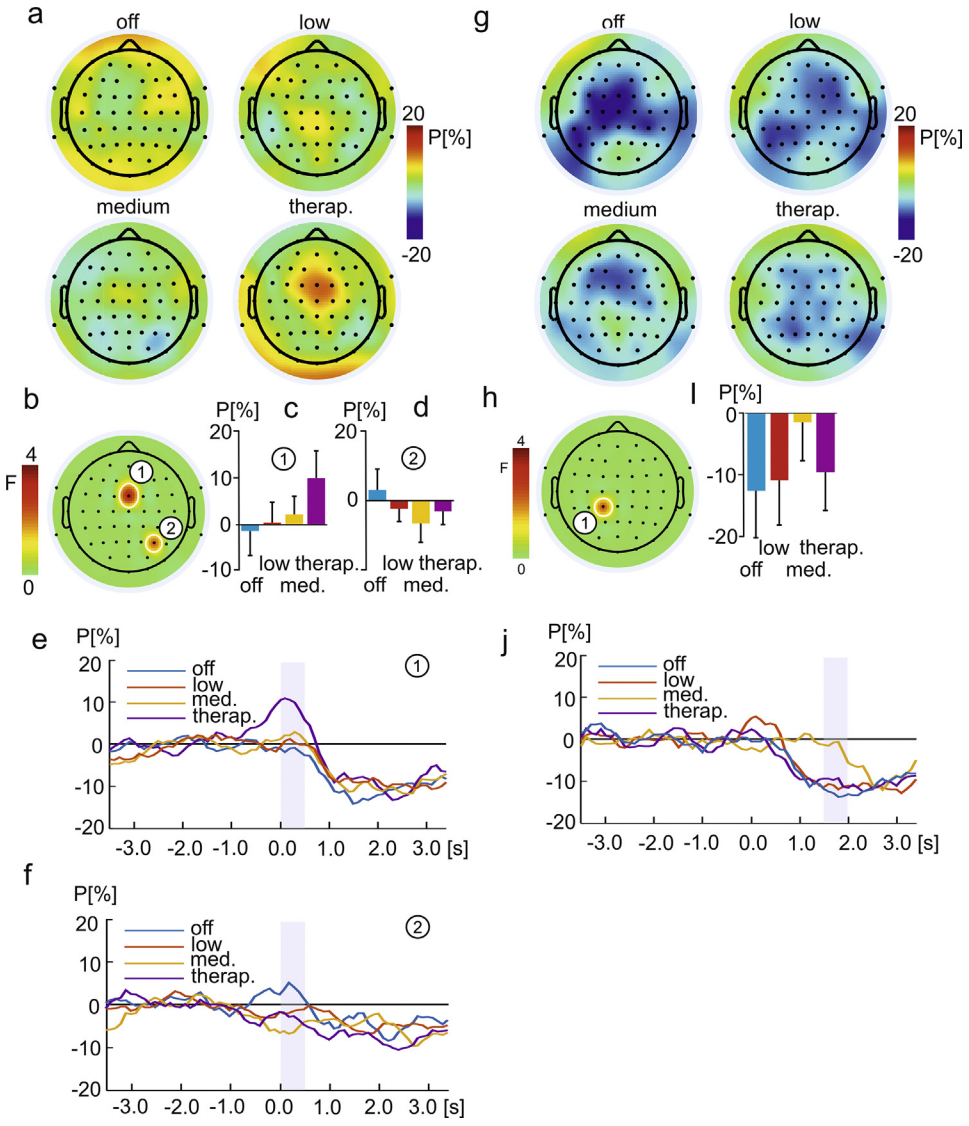

Figure 3. Effect of SCS intensity on 4–7 Hz band power during brushing. Topographic maps show the location of band-power changes during brushing at four intensities of SCS (off, low, medium, and the therapeutic level) in significant time bins at the onset of brushing (a) and in the middle of the brushing period (g), averaged over all participants ($N = 20$). Significant electrodes in the corresponding time bins were exported for statistical analyses (b and h). Bar charts (c, d, i) show percentage power change in the corresponding clusters. Error bars show SE of the mean. Time courses (e, f, j) show band-power changes over the duration of brushing for each cluster, with significant time bins highlighted in gray. [Color figure can be viewed at www.neuromodulationjournal.org]

Effect of SCS Intensity

The effect of intensity was evaluated separately for each frequency band using repeated measures ANOVAs in all time bins and electrodes of interest. Results of pairwise comparisons and cluster electrode locations for each contrast are shown in Supplementary Data Table S1.

4–7 Hz Band. Amplitude changes were observed in the 4–7 Hz band in frontal midline and right parietal electrodes in the latency 0.0 to 0.5 seconds, when the brush first touched the leg (Fig. 3a–f). The strongest effect of SCS intensity was seen in a frontal midline electrode ($F(3,57) = 4.22$, $p = 0.009$, $\varepsilon = 1.0$) owing to a 1-second band-power increase at brushing onset under the therapeutic compared with lower intensities ($p < 0.05$; Fig. 3c,e). The test of trend components confirmed a linear increase in band power with increasing SCS intensity ($F(1,19) = 9.32$, $p = 0.007$; Fig. 3c). This difference was not related to lower power in the baseline interval ($F(3,57) = 2.31$, $p > 0.05$). A smaller, statistically significant effect of SCS intensity was present in an electrode overlying the right parietal scalp region ($F(3,57) = 2.88$, $p = 0.044$, $\varepsilon = 1.0$; Fig. 3b) due to a brief increase in band power during no stimulation compared to medium intensity ($p < 0.05$; Fig. 3d,f).

Later in the brushing period (1.5–2.0 seconds), the medium intensity condition showed an absence of ERD which was observed in central-parietal regions in all other intensity conditions (Fig. 3g–j). A one-way repeated measures ANOVA confirmed a statistically significant effect of SCS intensity in a left central-parietal electrode ($F(3,57) = 2.95$, $p = 0.048$, $\varepsilon = 1.0$), with stronger ERD during no

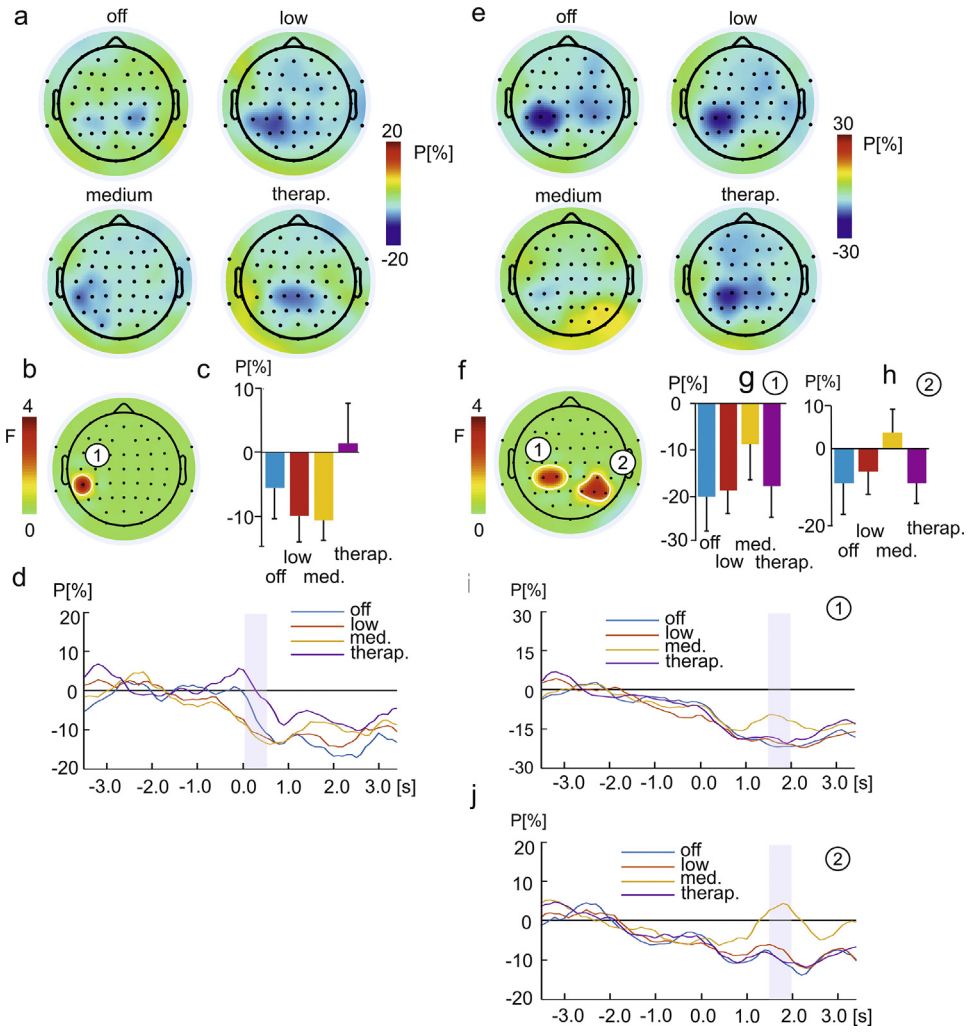

Figure 4. Effect of SCS intensity on 8–13 Hz band power during brushing. Topographic maps show the location of band-power changes during brushing at four intensities of SCS (off, low, medium, and the therapeutic level) in significant time bins at the onset of brushing (a) and in the middle of the brushing period (e), averaged over all participants ($N = 20$). Significant electrodes in the corresponding time bins were exported for statistical analyses (b and f). Bar charts (c, g, h) show percentage power change in the corresponding electrode clusters. Error bars show SE of the mean. Time courses (d, i, j) show band-power changes over the duration of brushing for each cluster, with significant time bins highlighted in gray. [Color figure can be viewed at www.neuromodulationjournal.org]

stimulation and low intensity compared to medium intensity ($p < 0.05$, Fig. 3h–i).

8–13 Hz Band. In the 8–13 Hz band, significant amplitude changes were found in a left parietal electrode in the 0.0–0.5–second epoch ($F(3,57) = 5.179$, $p = 0.007$, $\varepsilon = .791$; Fig. 4a–d). This effect was related to brief ERS at the strongest intensity compared with low and medium SCS intensities ($p < 0.05$; Fig. 4a). Approaching the middle of brushing (1.5–2.0 seconds), the medium intensity condition showed amplitude changes in left central-parietal and right parietal electrode clusters (Fig. 4e–j). A statistically significant effect was found in left central-parietal electrodes ($F(3,57) = 3.87$, $p = 0.015$, $\varepsilon = 0.949$) owing to a smaller band-power decrease at medium intensity SCS compared to low intensity and no stimulation ($p < 0.05$; Fig. 4g,i). Notably, right parietal electrodes showed a significant effect of intensity ($F(3,57) = 3.31$, $p = 0.044$, $\varepsilon = 0.701$) due to increased band power with medium intensity compared to no stimulation and therapeutic intensity ($p < .05$; Fig. 4h,j).

16–24 Hz Band. During the first second of brushing, repeated measures ANOVAs showed statistically significant amplitude changes in central and left midline electrodes. The strongest effect was found in frontal-central regions of the scalp at the start of brushing (0–0.5 seconds) ($F(3,57) = 3.32$, $p = 0.026$, $\varepsilon = 0.991$) due to decreased band power at medium intensity compared to low intensity and no stimulation ($p < 0.05$; Fig. 5a–d). Similarly, at 0.5 to 1.0 seconds ($F(3,57) = 3.1$, $p = 0.039$, $\varepsilon = 0.939$; Fig. 5e–h), band power was significantly reduced at moderate intensity SCS in central electrodes compared with low intensity and no stimulation ($p < 0.05$).

Approaching the middle of brushing stimuli at the latency of 1.5 to 2.0 seconds, there was a divergent effect of SCS intensity on 16–24 Hz band power (Fig. 5i–l). A statistically significant effect was found in right central-frontal electrodes ($F(3,57) = 3.69$, $p = 0.022$, $\varepsilon = 0.872$). This effect was due to decreased band power at low and therapeutic intensities compared to no stimulation ($p < 0.05$). In contrast, medium intensity SCS did not show a decrease in band

power relative to baseline power or compared with no stimulation ($p < 0.05$).

Toward the end of brushing, the two strongest SCS intensities showed a diminution of the robust band-power decrease observed in low intensity and no stimulation SCS in central and frontal regions of the scalp. An effect of SCS intensity was found at 2.5 to 3 seconds ($F(3,57) = 6.05$, $p = 0.002$, $\varepsilon = 0.923$), with a smaller reduction in band power at the two strongest SCS intensities compared to low intensity and no stimulation ($p < 0.05$; Fig. 5m–p). This effect was sustained toward the end of the brushing period (3–3.5 seconds) and extended to right frontal-central electrodes ($F(3,57) = 7.31$, $p < 0.001$, $\varepsilon = 1.0$; Fig. 5s–v), with a smaller band-power decrease at medium and therapeutic intensities compared to no stimulation and low intensity ($p < 0.05$). A significant effect of SCS intensity was found in parietal electrodes at 2.5 to 3.0 seconds ($F(3,57) = 3.25$, $p = 0.032$, $\varepsilon = 0.915$; Fig. 5p,r) owing to greater band power at medium intensity compared to the other three intensities ($p < 0.05$).

Interaction Between SCS Type and Intensity

No electrodes showing a significant main effect showed a statistically significant interaction between SCS type and intensity ($p > 0.05$).

DISCUSSION

The present study analyzed the effects of SCS type (burst, tonic) and intensity (off, low, medium, and therapeutic) on brushing-related changes in cortical oscillatory activity. Results demonstrate stronger 4–7 Hz and 8–13 Hz brushing-related ERD in burst compared to tonic SCS, with statistically significant effects in central, frontal, and parietal electrodes. SCS intensity modulated brushing-related ERD with a relatively weak ERD at greater SCS intensities, most notably at the medium SCS intensity. This effect was observed in central and parietal electrodes during early and middle periods of brushing stimulation in 4–7 Hz and 8–13 Hz bands, and in frontal and central electrodes during early and late periods of brushing in the 16–24 Hz band.

Tonic and burst SCS varied in the overall amount of brushing-related ERD, pointing towards a difference in the processing of afferent impulses from low-threshold mechanoreceptors. Attenuated 4–7 Hz and 8–13 Hz ERD during tonic SCS could indicate diminished cortical activation[27,31,53] due to parallel low-threshold mechanoreceptor input.[54–59] Therefore, results provide further support for the Gate Control Theory as the explanatory concept for tonic SCS.[8,11] In contrast, residual 8–13 Hz ERD in posterior parietal regions with tonic SCS may reflect activation of the primary sensorimotor foot area due to paresthesia.[60] Thus, attenuated brushing-related ERD suggests that tonic SCS may interfere with somatosensory processing by activating sensorimotor processing regions.

Burst SCS showed greater brushing-related ERD compared to tonic SCS in right frontal and left parietal electrodes in the 8–13 Hz band at the onset of brushing, and in right sensorimotor electrodes in the 4–7 Hz band towards the end of brushing. Sustained brushing-related ERD suggests engagement of the spinothalamic tract rather than the dorsal column during burst stimulation.[20,21] Analgesic effects of burst SCS have been suggested to result from greater modulation of affective and attentional aspects of pain via the medial pain pathway.[17,44] Decreased somatosensory alpha band power has been reported when attention is directed toward noxious and tactile stimuli,[61–64] suggesting a gating mechanism for relevant information. Comparatively, 4–7 Hz ERD towards the end of brushing may reflect recruitment of C-tactile fibers, with evidence that spectral changes and ultra-late potentials after gentle brushing stimuli peak at 2.5 seconds after brushing onset.[35] Ultra-late potentials have been linked to slow-wave responses from C-fibers transmitted by the spinothalamic tract.[35,65–68] Therefore, differences in brushing-related ERD between burst and tonic SCS may reflect greater spinothalamic tract involvement in burst compared to tonic SCS.

Effects of SCS intensity on brushing-related ERD were similar in both burst and tonic SCS. ERD was attenuated at medium intensity in left central-parietal electrodes in the 4–7 Hz and 8–13 Hz bands, and crucially at medium and therapeutic intensities in central midline, parietal, and frontal electrodes in the 16–24 Hz band. This finding suggests a nonlinear effect of SCS on somatosensory processing, with the weakest ERD reflecting the strongest interference with afferent impulses from low-threshold mechanoreceptors. Stronger ERD at medium-intensity conditions may be due to a ceiling effect of increasing stimulus intensities on ERD[69,70] or a potential overshoot in determining the most effective therapeutic parameters. Interestingly, nonlinear relationships between neurostimulation amplitude and outcomes have been previously demonstrated in experimental models of neuropathic pain. Quindlen-Hotek et al[71] showed the greatest decreases in anterior cingulate cortex responses to noxious and non-noxious brushing stimuli after burst SCS at 60% motor threshold, compared with 90% motor threshold. Similarly, greatest decreases in pain behavior have been reported with burst dorsal root ganglion stimulation at 50% and 66% motor threshold.[72] Combined, these findings suggest that lower SCS amplitudes, particularly in burst stimulation, may have the greatest effects on nociception.

In addition to attenuated ERD at medium and therapeutic intensities, 4–7 Hz ERS was sensitive to SCS intensity. At the onset of brushing, greater SCS intensities were associated with linear increases in 4–7 Hz ERS, particularly in frontal midline electrodes. Augmented resting theta power (4–7 Hz) has been consistently reported in chronic pain.[73–78] Dominant low-frequency oscillations in the thalamo-cortico-thalamic network have been proposed to be a contributing factor in the development or maintenance of several pathologies including chronic pain.[79,80] Changes in theta activity could be relevant for patient outcomes; increased prefrontal theta activity correlates with symptom severity in fibromyalgia,[77] and increased theta power in prefrontal, sensorimotor, and cingulate cortices occurs on cessation of tonic pain stimuli.[81] Thus, greater theta ERS with increasing SCS intensity could reflect an interference of neuropathic pain mechanisms.

In this study, brushing was applied to a pain-free area of the left or right leg. Comparisons between brushing side were not conducted in this study, as movement execution and somatosensory stimuli elicit bilateral ERD foci over sensorimotor cortices.[82–84] Previous investigation between movement of the right or left foot showed no significant differences in alpha band ERD.[83] Additionally, SCS for radicular pain after spinal surgery has been shown to increase cortical activation in the primary motor cortex somatotopically corresponding to the foot region,[60] located medially in the interhemispheric fissure.[85–87] Therefore, hemispheric differences in ERD between brushing locations were not anticipated.

A limitation of this study was the short duration of 2 minutes between intensity conditions. The washout period of tonic and

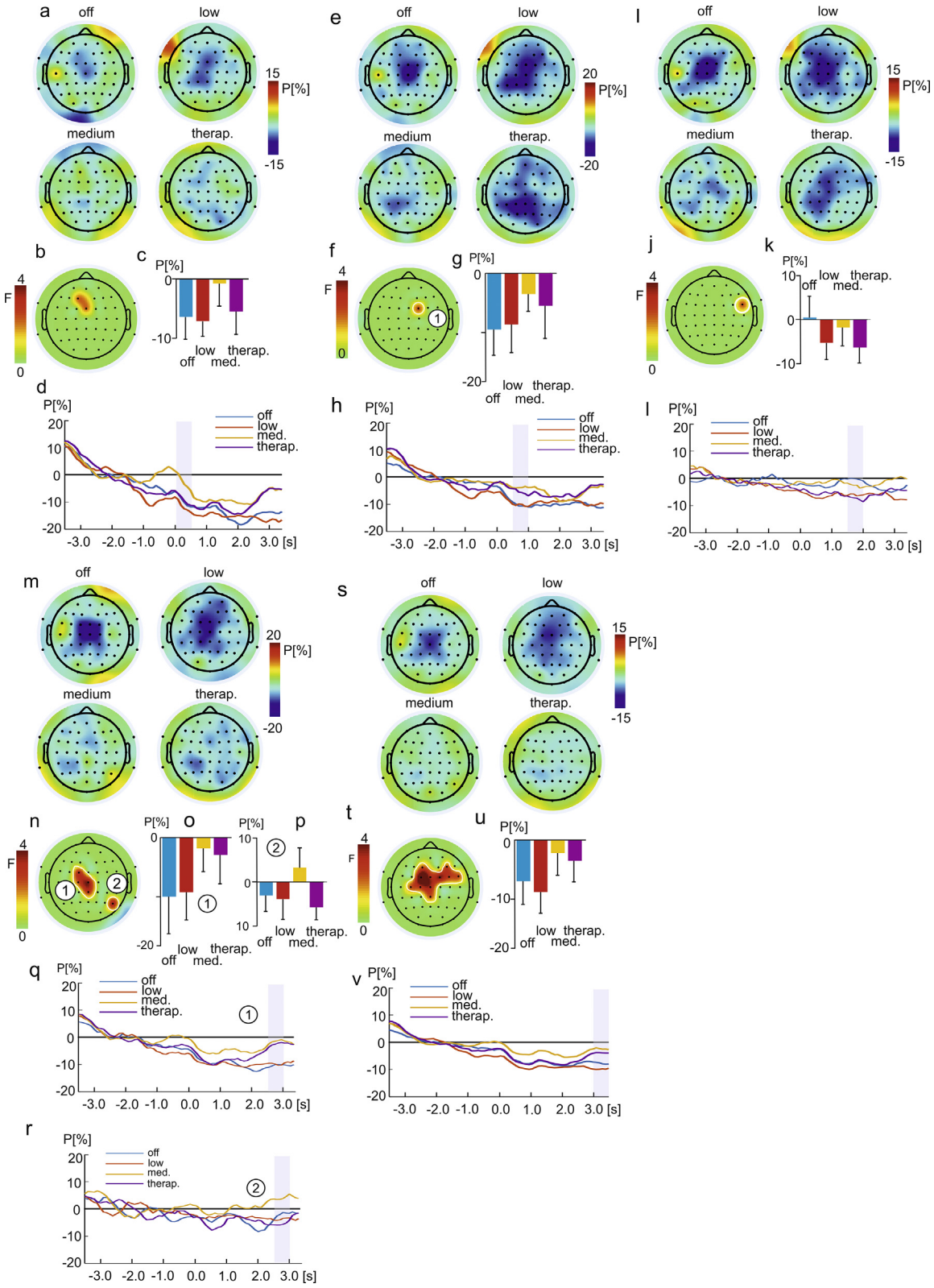

Figure 5. Effect of SCS intensity on 16–24 Hz band power during brushing. Topographic maps (a, e, i, m, s) show the location of band-power changes during brushing at four intensities of SCS (off, low, medium, and the therapeutic level) in statistically significant time bins, averaged over all participants ($N = 20$). Overhead views (b, f, j, n, t) show significant electrodes within the corresponding time bins that were exported for statistical analyses. Bar charts (c, g, k, o, p, u) show percentage power change in the corresponding electrode clusters. Error bars show SE of the mean. Time courses (d, h, l, q, r, v) show band-power changes over the duration of brushing, with significant time bins highlighted in gray. [Color figure can be viewed at www.neuromodulationjournal.org]

burst SCS is poorly understood and may differ according to stimulation type[88] or stimulus energy.[23,89] Delayed wash-in and prolonged washout periods have been indicated with active-recharge burst waveforms compared to tonic SCS.[88] Moreover, SCS dosing paradigms have recently been introduced, which alternate periods of stimulation with no stimulation,[90,91] suggesting that the effects of stimulation outlast the stimulation itself. Dosing waveforms have only been applied to burst SCS thus far and remain to be investigated with other SCS waveforms. To mitigate this effect, SCS intensities were varied in a pseudorandom order between participants and followed by a short washout period of no stimulation. Future studies could investigate differences between SCS intensities over a longer duration, which would allow greater disentangling of possible carryover effects.

Not unlike previous studies of supraspinal effects of SCS,[92] this study has a modest, heterogeneous sample. As SCS is used to relieve symptoms of neuropathic pain, rather than a specific pathology, divergent findings have been noted in the literature owing to the heterogeneity of patient groups.[93] In addition, large variability in treatment duration within patient groups was a limitation that could have potentially reduced the strength of group effects. Although no systematic difference in treatment duration was present, SCS duration did partially explain some of the variances in brushing-related ERD between burst and tonic SCS in two of four clusters in 4–7 Hz and 8–13 Hz bands. In a neuropathic pain model, short- and long-term effects of SCS were shown to have distinct mechanisms,[94] further investigation of which could shed light on the loss of efficacy observed in patients over time. Importantly, patients using burst and tonic SCS in this study were well matched on clinical characteristics such as pain intensity and symptom duration. Future investigations with larger populations should consider stratifying patients by pain phenotype and treatment duration to assess whether the observed effects differ across patient groups and over time.

There are potentially important implications for theory and clinical practice resulting from these findings. Tonic SCS appears to suppress parallel inputs from brushing stimuli, although as this study focused solely on the somatosensory component of SCS, it is not clear if this inhibitory effect would apply to the influence of SCS on nociceptive afferents. Future studies should investigate ERD patterns during burst and tonic SCS related to stimuli that primarily involve spinothalamic tract neurons, such as transient warming, cooling, or heat stimuli. Strong interference with the transmission of afferent impulses at SCS intensities as much as one-third less than the therapeutic level suggests that lower intensities may be more effective than the clinically programmed settings, in line with previous work in animals.[71,72] Our findings suggest that EEG may have a potentially valuable role in determining optimal stimulation parameters for relieving neuropathic pain.

CONCLUSIONS

To conclude, burst and tonic SCS modulate the cortical processing of tactile inputs differently, and changes in somatosensory processing may result from stronger involvement of the dorsal column system in tonic compared to burst SCS. Greater SCS intensities within the therapeutic limits may normalize aberrant cortical oscillations that are associated with neuropathic pain. However, intensities of SCS at 66% of the therapeutic level induced the strongest effects on cortical oscillations, suggesting that intensities lower than the therapeutic level may provide adequate pain relief whilst minimizing the likelihood of unwanted side effects. Results suggest that EEG analysis can yield an objective cue for determining the optimal SCS intensity.

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Authorship Statements

Danielle Hewitt was responsible for conceptualization, methods, software, investigation, formal analysis, writing—original draft, and writing—review and editing. Adam Byrne undertook investigation and writing—review and editing. Jessica Henderson undertook investigation and writing—review and editing. Kathryn Wilford worked on resources. Rajiv Chawla worked on resources. Manohar Lal Sharma worked on resources. Bernhard Frank worked on conceptualization, methods, resources, and funding acquisition. Nicholas Fallon undertook conceptualization and writing—review and editing. Christopher Brown worked on conceptualization and writing—review and editing. Andrej Stancak worked on conceptualization, methods, software, formal analysis, writing—original draft, writing—review and editing, supervision, and funding acquisition.

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SUPPLEMENTARY DATA

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