Heterogeneous Cortical Effects of Spinal Cord Stimulation

Bart Witjes, MSc[1] ⓘ **; Sylvain Baillet, PhD[2]; Mathieu Roy, PhD[3];**
Robert Oostenveld, PhD[4,5]; Frank J.P.M. Huygen, MD, PhD[1];
Cecile C. de Vos, PhD[1,2]

ABSTRACT

Objectives: The understanding of the cortical effects of spinal cord stimulation (SCS) remains limited. Multiple studies have investigated the effects of SCS in resting-state electroencephalography. However, owing to the large variation in reported outcomes, we aimed to describe the differential cortical responses between two types of SCS and between responders and nonresponders using magnetoencephalography (MEG).

Materials and Methods: We conducted 5-minute resting-state MEG recordings in 25 patients with chronic pain with active SCS in three sessions, each after a one-week exposure to tonic, burst, or sham SCS. We extracted six spectral features from the measured neurophysiological signals: the alpha peak frequency; alpha power ratio (power 7–9 Hz/power 9–11 Hz); and average power in the theta (4–7.5 Hz), alpha (8–12.5 Hz), beta (13–30 Hz), and low-gamma (30.5–60 Hz) frequency bands. We compared these features (using nonparametric permutation t-tests) for MEG sensor and cortical map effects across stimulation paradigms, between participants who reported low (< 5, responders) vs high (≥ 5, nonresponders) pain scores, and in three representative participants.

Results: We found statistically significant ($p < 0.05$, false discovery rate corrected) increased MEG sensor signal power below 3 Hz in response to burst SCS compared with tonic and sham SCS. We did not find statistically significant differences (all $p > 0.05$) between the power spectra of responders and nonresponders. Our data did not show statistically significant differences in the spectral features of interest among the three stimulation paradigms or between responders and nonresponders. These results were confirmed by the MEG cortical maps. However, we did identify certain trends in the MEG source maps for all comparisons and several features, with substantial variation across participants.

Conclusions: The considerable variation in cortical responses to the various SCS treatment options necessitates studies with sample sizes larger than commonly reported in the field and more personalized treatment plans. Studies with a finer stratification between responders and nonresponders are required to advance the knowledge on SCS treatment effects.

Keywords: Cortical activity, electroencephalography, magnetoencephalography, spectral features, spinal cord stimulation

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Address correspondence to: Bart Witjes, Center for Pain Medicine, Erasmus University Medical Center, PO box 2040, 3000 CA, Rotterdam, The Netherlands. Email: b.witjes.1@erasmusmc.nl

[1] Center for Pain Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands;
[2] Montreal Neurological Institute-Hospital, McGill University, Montreal, Canada;
[3] Department of Psychology, McGill University, Montreal, Canada;
[4] Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands; and
[5] NatMEG, Karolinska Institutet, Stockholm, Sweden

INTRODUCTION

Spinal cord stimulation (SCS), whose efficacy ranges from 48% to 81% (depending on, eg, the SCS paradigm used and pain etiology), is one possible treatment for chronic back and leg pain.[1–3] Electrical pulses are administered to the dorsal columns of the spinal cord, which carry sensory information from the source of pain. These electrical pulses induce paresthesia and modulate the pain signals.[4] The effectiveness of SCS treatment is difficult to predict before implantation because its neurophysiological mechanisms are not entirely understood. The working mechanism of conventional SCS is partially explained by the gate control theory.[5] More recently developed SCS paradigms deliver high-frequency tonic or burst stimulation and do not induce paresthesia,[6] with good pain relief compared with placebo.[7] Owing to the success of these paresthesia-free paradigms, recent studies have focused on supraspinal mechanisms of action, which are not well elucidated.[4] A better understanding of the cortical effects of SCS would provide insights into which patients would benefit from the therapy and by how much.

Stancak et al[8] used functional magnetic resonance imaging (fMRI) to study the effects of SCS in patients with persistent spinal pain syndrome type 2 (PSPS-T2; previously described as failed back surgery syndrome[9]). They observed increased activation of the medial primary sensorimotor, contralateral posterior insular, and ipsilateral secondary somatosensory cortices and decreased brain activity in bilateral primary motor, ipsilateral primary somatosensory, and anterior inferior temporal cortices during SCS.[8] Moens et al[10] also used fMRI to study the effects of short-term SCS and reported immediate pain relief through SCS, which correlated negatively with fMRI signal amplitude in the inferior olivary nucleus, cerebellum, and rostral anterior cingulate cortex.

Multiple electroencephalographic (EEG) studies have reported a reduction in somatosensory evoked potentials induced by SCS, suggesting that SCS inhibits cortical somatosensory processing.[11,12] However, the processing of experimentally applied somatosensory stimuli may differ from the processing of chronic pain. Multiple EEG studies have reported on the effects of SCS in resting-state recordings.[13] These studies were mostly exploratory, with small sample sizes (4–30 patients), and their findings varied considerably: modulations in each frequency band (delta [1–3.5 Hz], theta [4–7.5 Hz], alpha [8–12.5] Hz, beta [13–30] Hz, and gamma [30+ Hz]) have been mentioned in one or multiple studies. Activity in specific frequency bands could be indicative of specific cortical processes. For example, in healthy awake adults, alpha waves occur while quietly resting. Furthermore, modulation of alpha frequencies has been reported in the case of chronic pain.[14,15] The common findings of these EEG studies included the modulation of different pain pathways for paresthesia-free SCS paradigms compared with conventional tonic stimulation and increased alpha peak frequency, increased alpha power, or decreased theta power in SCS treatment compared with baseline.[13]

Schulman et al[16] studied theta and alpha frequency modulations using magnetoencephalography (MEG) and found a higher ratio of signal power in the lower alpha frequency band (7–9 Hz) to that in the higher alpha band (9–11 Hz) in patients with failed SCS than in healthy controls.[16] We recently replicated this finding;[15] using MEG's superior spatial resolution for source imaging we detected higher alpha power ratios in patients with PSPS-T2 than in healthy controls in several regions, including the occipital, parietal, temporal, and frontal lobes; insular and cingulate cortices; and right thalamus. We anticipate that effective SCS treatment, which reduces the perceived pain intensity, will normalize the alpha power ratios to those observed in healthy controls.

Because of the large variation in previously reported outcomes,[13] we assessed a broad range of spectral features and brain areas in our study. We investigated the cortical effects of two types of SCS (conventional tonic SCS vs paresthesia-free burst SCS) against a sham SCS condition using MEG source imaging. Because we expected to measure both the cortical responses to SCS and cortical markers of possible changes in pain intensity, we also examined the differential responses in participants reporting pain scores < 5 (responders) vs participants reporting pain scores ≥ 5 (nonresponders).[17] Because the large variation in outcomes between studies suggests a large variety in cortical responses between patients, we also explored treatment effects in three representative participants.

MATERIALS AND METHODS

Participants

Twenty-five patients with chronic pain with SCS participated in this study. The inclusion criteria required that the participants were aged 18 years, had had active SCS over at least the past 3 months with a stable pain response to the stimulation, and had a pulse generator implanted in the lower body that can be programmed to deliver burst stimulation, with an implanted electrode lead at spinal level Th8 or below. Exclusion criteria were severe pain sensations in addition to the SCS target pain and any other form of severe decline in general health.

Patients were recruited from pain clinics in the Netherlands (Medisch Spectrum Twente [Enschede], Erasmus University Medical Center [Rotterdam], Sint Maartenskliniek [Nijmegen]) and Canada (Montreal Neurological Institute and Hospital and Hôpital Maisonneuve-Rosemont [Montreal]). Ethics approval was obtained from the Institutional Review Boards of the Montreal Neurological Institute (Montreal, Canada) and the CMO region Arnhem–Nijmegen (The Netherlands); all participants provided written informed consent to participate in the study.

Data Acquisition

The study protocol comprised four visits with one-week intervals. During the baseline visit, a nurse practitioner programmed the patient's stimulator for three stimulation paradigms in a randomized order: (conventional) tonic, burst, and sham stimulation. At their next visit in the following week, participants' brain activity was recorded using MEG during their active SCS. After the MEG session, the stimulators were programmed to deliver the second stimulation paradigm. The third follow-up visit proceeded identically, with another MEG recording during active SCS and the stimulator switched to the third and last stimulation paradigm. Both the investigator and the participants were blinded to the type of stimulation corresponding to the stimulator programs 1, 2, and 3. The parameters of the tonic and burst stimulation programs were those established by standard-of-care guidelines. Sham stimulation was programmed with the same electrode configuration as burst stimulation but delivered only two pulses (instead of five) at the lowest possible amplitude (0.05 mA). Therefore, sham stimulation was expected to produce a nontherapeutic effect. The participants were instructed to maintain a diary between visits to report pain

scores on a 0 to 10 numeric rating scale (NRS) and describe the perceived effects of each stimulation paradigm.

Before each MEG session, the participants answered standard questionnaires in their preferred language (Dutch, English, or French) concerning pain (the Brief Pain Inventory), generic health status (EuroQol 5 dimensions 5 levels [EQ5D]), and their state of anxiety and depression (the Hospital Anxiety and Depression Scale [HADS]). We report below the EQ5D data using index values, with the crosswalk value set from the relevant country (Netherlands or Canada). HADS scores were computed separately from the anxiety and depression questions. Medication usage was divided between opioids, adjuvant analgesics (antiepileptic drugs, antidepressants, etc), and nonsteroidal anti-inflammatory drugs.

The MEG sessions consisted of 5-minute resting-state recordings conducted at the Montreal Neurological Institute (McGill University, Montreal, Canada) or the Donders Institute for Brain, Cognition and Behavior (Nijmegen, The Netherlands). The MEG systems (CTF, Coquitlam, British Columbia, Canada), acquisition software, and measurement setups were identical at both locations. The participants were seated upright under the 275-channel whole-head MEG system inside a passive magnetically shielded room. Before entering the room, the participants changed into scrubs and were instructed to remove any metal materials, to ensure optimal data quality. The data sampling rate was 2400 Hz (built-in antialiasing lowpass filter with a 600 Hz cutoff), and third-order gradient compensation was applied for MEG noise reduction. Reference signals for ocular and cardiac artifacts were captured from horizontal and vertical electrooculogram and electrocardiogram electrodes. The participant's head position in the MEG helmet was registered using three head coils attached to three anatomical landmarks: nasion and left/right preauricular points. We used a three-dimensional digitizer system (Polhemus Isotrak, Colchester, Vermont) to digitize the participant's head shape, the respective locations of the head-positioning coils, and anatomical landmarks. We conducted a 2-minute empty-room recording to capture environmental noise before every individual session and to inform the MEG source modeling process.[18] The participants were instructed to sit still with their eyes open, maintaining their gaze on a fixation cross.

Data Analysis

All data processing was performed using Brainstorm using MATLAB version R2020a (The MathWorks, Natick, MA).[19] Brainstorm is an open-source application freely available under the GNU general public license (http://neuroimage.usc.edu/brainstorm). We used the recommended processing pipeline for MEG preprocessing in Brainstorm, following good practice guidelines.[20,21] We used the data processing pipeline reported in our previous study.[15]

We derived the power spectral densities (PSDs) of preprocessed MEG recordings using Welch's method, with a 4-second Hamming sliding window and 50% overlap. PSDs were normalized to the total signal power across 1 to 62 Hz, because different notch filters were applied for recordings in The Netherlands (50 Hz powerline) and Canada (60 Hz powerline). When SCS artifacts were present in the signal, a notch filter was applied at the SCS frequency, which varied between participants.

We computed the average PSD across all sensors to inspect global groupwise differences. We then extracted six spectral features from the resulting average PSDs: the alpha peak frequency (maximum power 7–13 Hz); the alpha power ratio[15] (power 7–9 Hz divided by power 9–11 Hz); and the average power across the theta (4–7.5 Hz),

alpha (8–12.5 Hz), beta (13–30 Hz), and low-gamma (30.5–60 Hz) frequency bands. The alpha peak frequency was defined as the frequency bin with maximum power in the 7 to 13 Hz range.

We also derived these features from MEG source maps. We used Brainstorm to adjust the ICBM152 T_1-weighted magnetic resonance imaging template[22] to the digitized head shape of each participant via affine transformations, to obtain a three-dimensional grid of elementary MEG sources consisting of 11,467 current dipoles evenly distributed across the entire brain volume. We obtained MEG forward head models for each participant using the overlapping sphere method.[23] We then derived the MEG source time series at each brain location using dynamic statistical parametric mapping with Brainstorm's default parameter values. We allocated each of the 11,467 MEG sources to a parcel of the automated anatomical labeling (AAL) atlas[24] using Brainstorm procedures. The average MEG source time series from each AAL brain region was extracted and subjected to the spectral analysis used for the sensor time series as described above.

Comparisons and Subgroups

To disentangle the effects of the SCS paradigm and perceived pain intensity on brain activity, we compared the MEG spectral features across SCS paradigms and, separately, between effects of SCS on pain. To study the effects of stimulation paradigm (independent of treatment effect), we compared the spectral features between tonic, burst, and sham stimulation. To study the analgesic effect of the treatment (independent of SCS paradigm), we compared the spectral features of MEG recordings in which the participants reported low pain intensity vs the recordings in which the participants reported high pain intensity. We pooled the recordings with tonic and burst SCS for all patients and split the resulting data set into recordings of patients who reported an NRS pain score < 5 (responders) and ≥ 5 (nonresponders).[17]

We observed large variations in reported outcomes[13] and variable individual responses to the different SCS paradigms in our sample. Such strong interindividual variability may be detrimental to the sensitivity of group average analyses. We therefore explored whether the monitoring of treatment effect could be derived at the level of individual patients. We evaluated the effects of SCS in three representative participants: one responder to burst SCS, one responder to tonic SCS, and one nonresponder to any of the tested SCS paradigms. These individuals were selected on the basis of their reported NRS score: the SCS responders reported a reduction of at least 50% in their NRS score after tonic or burst SCS compared with sham stimulation. We then compared the PSDs and alpha power ratios in the tonic, burst, and sham SCS conditions.

Statistical Analysis

Differences in EQ5D, HADS anxiety, and HADS depression scores between SCS paradigms were tested using a repeated measures ANOVA. We used Mauchly's test for sphericity; if the assumption of sphericity was violated, we reported the Huynh-Feldt corrected values. Normal distribution was verified by plotting histograms of the EQ5D, HADS anxiety, and depression scores.

For testing effects in the sensor-averaged spectral features, we used independent permutation t-tests after verifying a normal distribution by plotting histograms of these features. For testing sensor-averaged power spectra and spectral effects in AAL brain regions, we used nonparametric permutation t-tests (10,000 permutations) with Monte Carlo random sampling.[25,26] For all tests,

Table 1. Participant Characteristics.

Participant	Age, y	Sex	Pain duration, y	Pain location	NRS tonic	NRS burst	NRS sham	Opioid	Adjuvant analgesics	NSAID
PT01	53	M	32	Back and left leg	0	0	1	Yes	Yes	Yes
PT02	74	F	50	Back	6	7	6	No	Yes	No
PT03	42	F	20	Right hip and buttock	4	2	5	Yes	Yes	No
PT04	59	M	6	Back and left leg and foot	7	5	5	No	Yes	No
PT05	52	M	5	Right hip, buttock, leg, and foot	6	7	6	Yes	Yes	No
PT06	45	F	16	Back	1	2	3	Yes	Yes	No
PT07	58	M	31	Back and left leg	3	2	3	No	Yes	Yes
PT08	42	F	19	Back and left hip, buttock, and leg	4	2	2	Yes	Yes	No
PT09	62	F	12	Back, neck, and right buttock and leg	6	9	4	Yes	Yes	Yes
PT10	70	M	15	Both feet	6	4	6	Yes	No	No
PT11	62	F	20	Back and right buttock, and leg	6	6	5	Yes	Yes	No
PT12	60	M	> 4	Right leg	8	8	9	No	No	No
PT13	55	M	18	Back and Right leg	3	4	3	Yes	No	No
PT14	52	M	4	Right leg and foot	6	5	6	No	No	No
PT15	43	F	23	Back and left leg and foot	4	3	3	Yes	No	No
PT16	64	M	9	Back	6	2	6	No	No	No
PT17	70	M	21	Right leg, buttock, and foot	1	1	1	No	No	No
PT18	56	F	3	Back and left foot	7	7	—*	Yes	Yes	Yes
PT19	40	F	5	Right leg and foot	2	5	6	Yes	No	No
PT20	56	F	35	Back and right leg	3	2	5	Yes	No	No
PT21	49	F	13	Left leg, buttock, and foot	5	5	6	No	No	No
PT22	63	M	15	Back and left leg	2	7	2	Yes	No	No
PT23	53	M	15	Back and left leg	4	—†	7	No	Yes	No
PT24	68	M	29	Right back and buttock	2‡	3‡	3‡	No	No	No
PT25	60	M	40	Left back, buttock, and leg	7*	6	2	Yes	No	No

F, female; M, male; NSAID, nonsteroidal anti-inflammatory drugs.

*For this patient, the sham recording was missing.

†For this patient, it was not possible to program burst stimulation.

‡Excluded for poor data quality.

the observed effects were considered statistically significant when the associated corrected p value was < 0.05.

To test the effects of stimulation paradigms, we performed paired permutation t-tests separately for tonic vs burst, tonic vs sham, and burst vs sham SCS. To test the effects of treatment, we performed an independent permutation t-test between responders and non-responders. For the permutation t-tests of differences in peak frequency and alpha power ratio, we applied a false discovery rate (FDR) correction for the 94 brain regions. For testing the frequency-band–specific power, we applied an FDR correction for the 94 brain regions and the four frequency bands.[27] Because considerable interindividual variability was expected in response to the different SCS paradigms (as previously reported), we also explored differences without FDR correction ($p < 0.05$) for the tested brain regions.

RESULTS

Demographics

In total, 25 participants were enrolled in the study: 11 in Canada and 14 in The Netherlands. One participant was excluded because of insufficient MEG data quality due to dental implant artifacts. For another participant, the data in the tonic SCS condition was excluded because of insufficient MEG data quality. The burst SCS paradigm could not be programmed in the stimulator for one participant, who therefore was examined only in the other two conditions. For another participant, the sham stimulation could not be programmed. Overall, MEG data from 24 participants were usable, with a complete data set in all three SCS conditions available for 21 participants (Table 1).

The EQ5D, HADS anxiety, and HADS depression scores for tonic, burst, and sham sessions for each participant are shown in Supplementary Data Table S1. A repeated-measures ANOVA did not show statistically significant differences between the SCS paradigms (Supplementary Data Table S1).

Effects of Stimulation Paradigms

The average NRS pain score across all participants was similar for each paradigm (4 ± 2; mean ± SD). However, participants showed considerable variation in the NRS pain scores (Table 1). We did not find statistically significant differences in the spectral features between the SCS paradigms after multiple comparison correction (tonic vs burst, tonic vs sham, burst vs sham).

Sensor-Level Analyses

Figure 1 shows the whole-head sensor-averaged PSDs in the tonic, burst, and sham conditions. We found statistically significant increased signal power below 3 Hz for burst vs tonic and burst vs sham (paired t-tests; $p < 0.05$). None of the sensor-averaged spectral features (peak frequency, average power in frequency bands, or alpha power ratio) were statistically different between stimulation paradigms but showed substantial interindividual variability (Supplementary Data Fig. S1).

Brain-Level Analyses

No statistically significant differences were found in the alpha peak frequency, average power in tested frequency bands, or alpha power ratio across brain regions between SCS conditions. We then explored differences without FDR correction between the stimulation paradigms and detected trends ($p < 0.05$ without FDR correction) in multiple regions for all three comparisons (Fig. 2). A complete overview of the trends per brain area and spectral feature is provided in Supplementary Data Table S2.

Comparing burst vs tonic without FDR correction, we found trends for the alpha peak frequency (higher for burst), alpha power ratio (lower for burst), and average power in all tested frequency bands (lower for burst) in multiple brain areas. Comparing burst vs sham without FDR correction, we detected trends for the alpha peak frequency (higher for burst), alpha power ratio (lower for burst), and average power in all
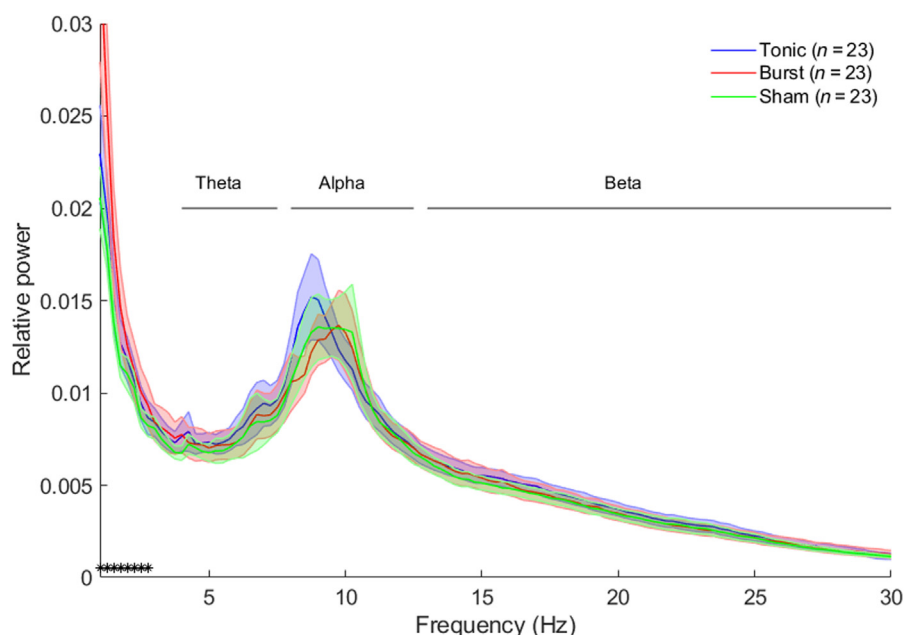

Figure 1. Relative PSD for tonic, burst, and sham stimulation; shaded areas represent SE. *A paired t-test showed significantly increased signal power ($p < 0.05$) below 3 Hz for burst vs tonic and for burst vs sham. Tonic vs sham did not show significant differences. We zoomed in on the frequency range 1 to 30 Hz because after 30 Hz, the lines were overlapping. [Color figure can be viewed at www.neuromodulationjournal.org]
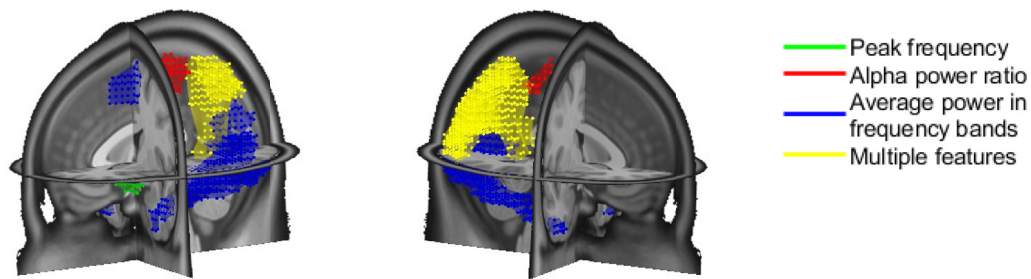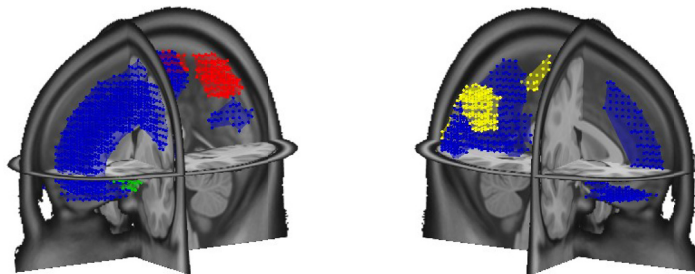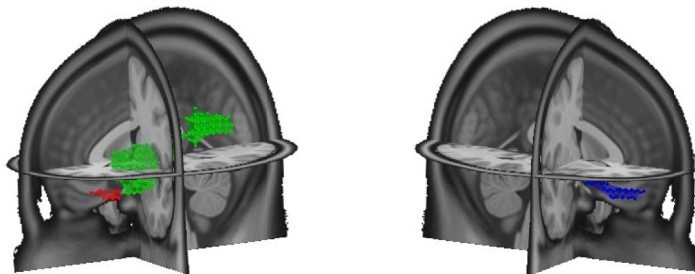
Burst vs tonic

Burst vs sham

Tonic vs sham

Figure 2. Brain regions that showed trends ($p < 0.05$ without multiple comparisons correction for the tested brain regions) for the comparisons of burst and tonic stimulation, burst and sham stimulation, and tonic and sham stimulation. A complete overview of the trends per area is shown in Supplementary Data Table S2. Brain areas where multiple features showed trends are highlighted in yellow. Areas where multiple features showed trends for burst vs tonic were the right angular gyrus (theta and beta power and alpha power ratio), right posterior cingulate gyrus (theta power and peak frequency), right cuneus (theta, alpha and beta power, and alpha power ratio), right middle occipital gyrus (theta and alpha power and alpha power ratio), right superior occipital gyrus (theta power and alpha power ratio), left and right superior parietal gyrus (theta power and alpha power ratio), left precuneus (theta and beta power and alpha power ratio), and right precuneus (theta power and alpha power ratio). Areas where multiple features showed trends for burst vs sham were the right angular gyrus (peak frequency and alpha power ratio), right superior occipital gyrus (theta power, peak frequency, and alpha power ratio), and right paracentral lobule (theta and beta power and alpha power ratio). Areas where multiple features showed trends for tonic vs sham were the left insula (peak frequency), the left lateral orbital gyrus (alpha power ratio), the right gyrus rectus (alpha power), and the left supramarginal gyrus (peak frequency). [Color figure can be viewed at www.neuromodulationjournal.org]

tested frequency bands (lower for burst). Comparing tonic vs sham without FDR correction, we found trends for the alpha peak frequency (lower for tonic), alpha power ratio (lower for tonic), and average power in the alpha band (lower for tonic).

Analgesic Effects of SCS

To compare between SCS responders and nonresponders, we divided all tonic and burst recordings into those in which the participants reported an NRS score < 5 ($n = 23$) and ≥ 5 ($n = 23$). No statistically significant differences were found in the alpha peak frequency,

average power in tested frequency bands, and alpha power ratio across brain regions between responders and nonresponders.

Sensor-Level Analyses

Figure 3 shows the whole-head sensor-averaged PSDs for responders ($n = 23$) and nonresponders ($n = 23$); an independent t-test did not show statistically significant differences between the two groups. None of the six sensor-averaged spectral features were statistically different between responders and nonresponders (Supplementary Data Fig. S2).
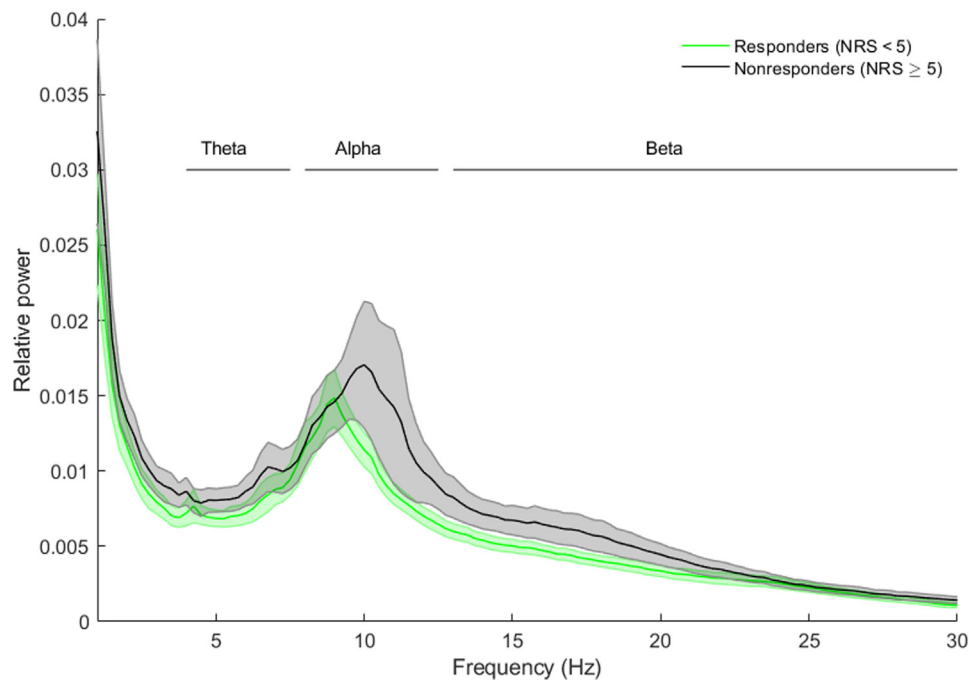
Figure 3. Relative PSD for responders (recordings in which patients reported NRS < 5, n = 23) and nonresponders (recordings in which patients NRS ≥ 5, n = 23); shaded areas represent SE. An independent *t*-test did not show significant differences between the two groups. We zoomed in on the frequency range 1 to 30 Hz because after 30 Hz, the lines were overlapping. [Color figure can be viewed at www.neuromodulationjournal.org]

Brain-Level Analyses

We did not find statistically significant differences in the alpha peak frequency, average power in tested frequency bands, and alpha power ratio across brain regions between responders and nonresponders. Comparison between responders and nonresponders without FDR correction (Fig. 4) showed trends for the alpha peak frequency (lower for responders) and average power in beta band (lower for responders).

Effects on Representative Participants

Sensor-Level Analyses

Figure 5 shows the whole-head sensor-averaged PSDs for tonic and burst stimulation in three representative participants. In the tonic SCS responder (PT06, age 45 years, female, using opioids and adjuvant analgesics), the PSD showed higher alpha peak power for burst stimulation than for tonic stimulation. In the burst SCS responder (PT16, age 64 years, male, not using medication), the PSD showed lower overall relative power and lower alpha peak power for burst stimulation. In the nonresponder (PT02, age 74 years, female, using adjuvant analgesics), the PSD showed lower alpha peak power for both conditions than in the responders.

For the tonic SCS responder, the whole-head sensor-averaged alpha power ratio was 2.4 for tonic SCS and 2.5 for burst and sham SCS. For the burst responder, the ratio was 1.1, 0.9, 1.4 for tonic, burst, and sham SCS, respectively. For the nonresponder, the alpha power ratio was 0.8 for tonic and burst SCS and 0.7 for sham SCS.

Brain-Level Analyses

The alpha power ratios for each voxel in the brain for the three participants are shown in Figure 6. The tonic SCS responder showed similarly high alpha power ratios for burst and sham SCS, and the alpha power ratios for tonic SCS were slightly lower in temporal regions. The burst SCS responder showed lower ratios for burst SCS than for tonic and sham SCS. The nonresponder showed similar alpha power ratios between conditions, but they were lower than those in the responders (note that the colored bars have different scales).

DISCUSSION

Main Findings

We compared MEG spectral features in patients across different SCS paradigms and with different treatment effects. We only found statistically significant differences ($p < 0.05$, FDR corrected) between different SCS paradigms in the 1 to 3 Hz frequency range. Other spectral comparisons did not show statistically significant differences likely owing to large interindividual differences. Our data emphasize the need for studies with larger sample sizes and finer stratification between responders and nonresponders and more personalized treatment plans for chronic pain patients.

Effects of Stimulation Paradigms

We found statistically significant higher signal power below 3 Hz ($p < 0.05$, FDR corrected) in burst SCS than in tonic SCS and sham SCS. Previous EEG studies in patients with SCS have also reported differences in the delta frequency range.[28–30] Goudman et al[30] found increased sensor-averaged power in the 1 to 8 Hz range in the high-density SCS compared with the tonic SCS and baseline (preimplantation). Buentjen et al[29] found decreased sensor-averaged power in the 1 to 6 Hz range when comparing the burst and tonic SCS vs SCS switched off, which is contrary to our findings for burst vs tonic SCS and burst vs sham SCS. However, the delta frequency range may be affected by noise in M/EEG studies. Some of our recordings contained large artifacts owing to metallic
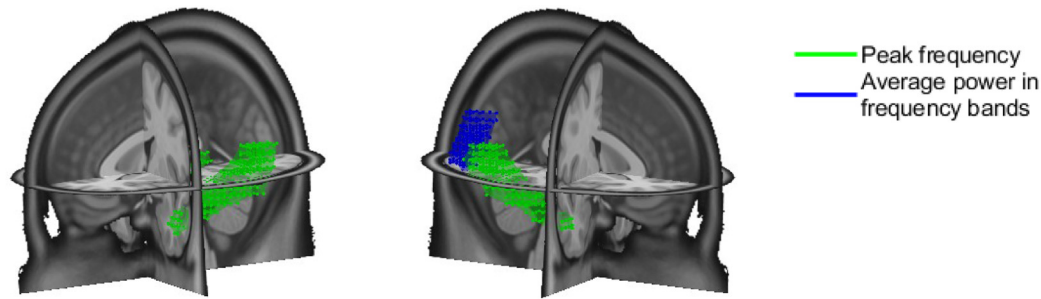
Figure 4. Brain regions that showed trends ($p < 0.05$ without multiple comparisons correction for the tested brain regions) for the comparison of responders ($n = 23$) with nonresponders ($n = 23$). Areas where the peak frequency showed trends were the left Heschl gyrus and left and right middle temporal gyrus. The right middle occipital gyrus showed a trend for the beta power. [Color figure can be viewed at www.neuromodulationjournal.org]

dental implants. Although we had mostly removed these artifacts and these artifacts were present to a similar degree in all three conditions, some low-frequency noise might have affected our results. In the source-level analyses, we did not find statistically significant differences in the delta frequency range; therefore, we could not identify the brain region responsible for this difference.

Other analyses of our MEG data demonstrated no statistically significant differences, in contrast with multiple EEG studies that reported one or more differences in the theta, alpha, beta, and gamma frequency ranges between SCS paradigms.[13,28–35] However, there were large variations in these outcomes between studies likely because of the large variation in the study design, SCS paradigms, analysis methods, and brain areas and spectral features studied.[13] These EEG studies had small sample sizes, with seven of the eight studies including ≤ 10 patients and used different multiple comparison correction methods, which may explain the disparity in the findings. Although the present study included 25 representative patients of the SCS patient population in our clinics

(in terms of pain etiology, medication, NRS pain score, SCS paradigm used and age), previously reported findings could not be reproduced. The lack of statistically significant results in our study may be attributable to substantial interindividual differences in the NRS, EQ5D, and HADS scores; medication usage; and MEG spectral features studied. For both tonic and burst stimulation, the group-averaged NRS scores were similar and both responders and nonresponders were included. Thus, the diverse group of SCS patients in this study showed no statistically significant effects, whereas other studies with smaller samples did report effects.

We explored trends in our data without multiple comparison correction. The PSDs for the SCS paradigms suggested a lower alpha peak frequency for tonic stimulation than for burst stimulation, which was not reported in previous studies. We could not relate the trends in brain activity to previous studies comparing burst and tonic, burst and sham (stimulation switched off), or tonic and sham (stimulation off) stimulations.[13] This further underlines the large heterogeneity in findings, emphasizing the need for
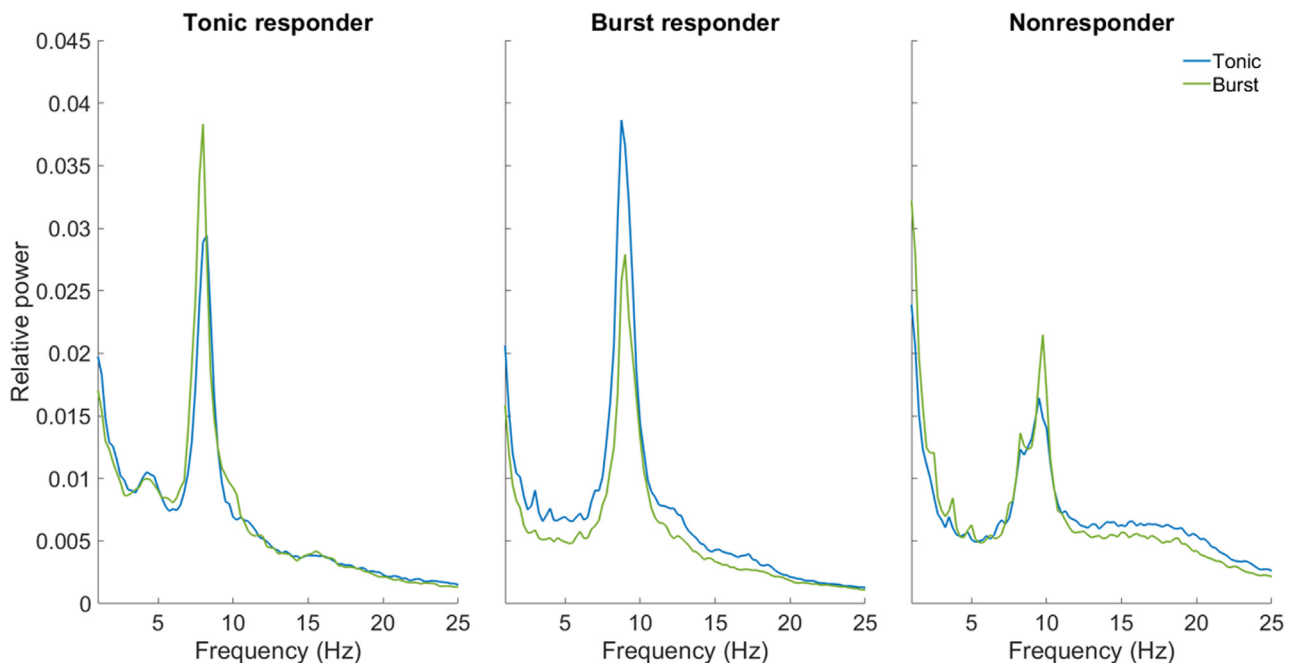

Figure 5. Sensor-average PSD of the therapeutic sessions (tonic and burst SCS) for a responder to tonic stimulation (PT06), a responder to burst stimulation (PT16), and a nonresponder to SCS (PT02). Only data in the 1 to 25 Hz frequency range are shown, because no differences were visible beyond 25 Hz. [Color figure can be viewed at www.neuromodulationjournal.org]
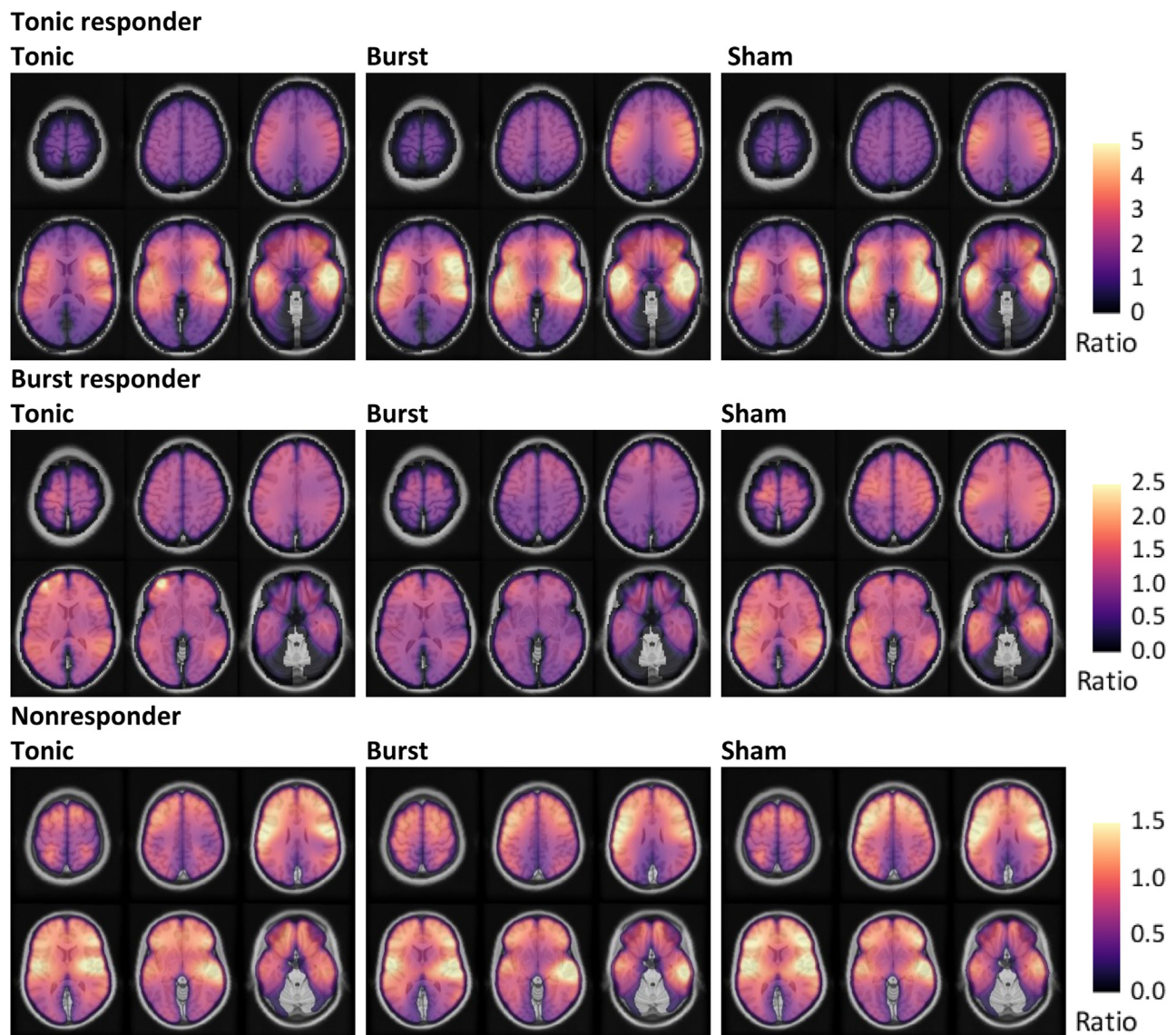
Tonic responder

Figure 6. The alpha power ratio for each voxel in six different magnetic resonance imaging slices for a responder to tonic stimulation (PT06), a responder to burst stimulation (PT16), and a nonresponder to SCS (PT02). Note that the colorbar is different for each individual. The tonic responder reported an NRS of 1 for tonic stimulation, 2 for burst stimulation, and 3 for sham stimulation. The burst responder reported an NRS of 6 for tonic, 2 for burst, and 6 for sham stimulation and the nonresponder reported an NRS of 6 for tonic, 7 for burst, and 6 for sham stimulation. [Color figure can be viewed at www.neuromodulationjournal.org]

careful patient selection for group analyses and the need for individualized treatment monitoring.

Analgesic Effects of SCS

No statistically significant differences in brain activity were detected between recordings in which participants reported an NRS score < 5 or ≥ 5, regardless of the stimulation setting. This may be because the nonresponders (NRS ≥ 5) showed a large SE in the PSD. Despite the large variability, the average PSD showed a higher alpha peak frequency in the nonresponders than in the responders. This is contrary to the expectation because alpha peak frequency is reported to be reduced in cases of neuropathic pain.[14,36–40] Furthermore, our previous study[15] found higher alpha power ratios in patients with chronic pain than in pain-free controls, indicating relatively higher power in the lower alpha frequency range. Schulman et al[16] found that the ratios in patients with

successful SCS were more similar to controls and the ratios in patients with failed SCS were more similar to patients with chronic pain. Therefore, we expected lower peak frequencies in the painful condition than in the nonpainful condition.

Previous studies[28–33] focused on the trial SCS period or a period immediately thereafter; in contrast, our participants had received SCS for at least 6 months, up to > 10 years. Because we included only patients already implanted with an SCS system, we could not compare their neurophysiological data with preimplantation baseline data. Ideally, we would define responders and nonresponders based on pain reduction with respect to baseline data. However, because this data was not available, we defined responders and nonresponders on the basis of absolute NRS scores. We chose a cutoff NRS score of 5, which is an eligibility criterion for patients to as SCS trial.[17] All participants who reported NRS <5 experienced a reduction in NRS pain score with respect to

(preimplantation) baseline. We chose the absolute NRS scores over the changes in NRS score compared with sham stimulation, because the changes in pain scores reported by participants across the SCS paradigms were relatively small. Moreover, the sham condition did not always result in higher NRS scores, possibly because the stimulation was not entirely switched off in this condition. We speculate that this lowest possible SCS amplitude still has therapeutic effects in some patients. Furthermore, we can speculate that only one week between switching SCS paradigms may not be sufficient for the cortical effects of the previous paradigm to subside, especially because most participants had been receiving SCS for a long time.

Because medication usage and time since implantation varied between patients, these factors may have influenced our grouping of responders and nonresponders. However, the recordings were pooled before splitting the group into responders and nonresponders, and they did not change their medication regimen in the course of their participation in the study.

In this study, post hoc Pearson correlation analyses between the NRS scores and each of the six spectral features did not show any trends. In future studies, adding multiple measures (eg, EQ5D and HADS scores, medication usage, etc) to the comparison of responders and nonresponders would provide more insights on the differences in cortical activity. Larger groups of responders and nonresponders to each SCS paradigm, preferably in comparison with preimplantation MEG baseline recordings, are necessary to assess these differences in brain activity with greater sensitivity.

Effects on Representative Participants

Exploration of effects in the three representative participants showed three different patterns of sensor-averaged PSDs. The responders showed lower alpha peak power in the SCS paradigm for which they reported the lowest NRS score. The nonresponder showed lower alpha peak power in both settings than the responders and a slightly lower alpha peak power for tonic SCS (NRS score 6) than for burst SCS (NRS score 7). In summary, the lower the NRS score, the lower the alpha peak power. Therefore, for within-subject comparisons, the alpha peak power may be related to the NRS score.

We found only minor differences in alpha power ratios. The tonic SCS responder showed slightly lower alpha power ratios in the temporal cortices for tonic stimulation than for burst and sham stimulation. The burst SCS responder also showed lower alpha power ratios primarily in the temporal, central, and parietal cortices for burst stimulation than for tonic and sham stimulation. The nonresponder showed similar alpha power ratios across all three conditions. The substantial differences in the alpha power ratio among these three participants suggests that this feature is not suitable for comparisons between participants. The differences observed in the burst SCS responder indicate that this feature is informative of treatment response to different SCS paradigms in specific brain areas in a single participant. However, because there were no considerable differences in the tonic responder, this feature may also be influenced by factors other than pain intensity. It remains challenging to disentangle the effects of pain relief from those of the stimulation itself.

CONCLUSIONS

We used MEG to compare various spectral features in cortical activity in 24 patients with SCS. We compared the effects of tonic,

burst, and sham stimulation and compared between responders and nonresponders. We performed source imaging, but only found statistically significant differences in the sensor-averaged PSDs for burst vs tonic and burst vs sham stimulation. Owing to the large diversity of treatment responses per SCS paradigm, larger sample sizes and finer stratification between responders and nonresponders are required to further assess SCS treatment effects. Furthermore, the differences observed in representative participants and substantial variation in SCS treatment response in patients emphasize the need for personalized treatment plans.

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Authorship Statements

Bart Witjes and Cecile C. de Vos designed and conducted the study, including patient recruitment, data collection, and data analysis. Sylvain Baillet and Mathieu Roy provided important input regarding data analysis. Bart Witjes prepared the manuscript draft. All authors were involved in editing of the manuscript and approving the final manuscript.

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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.2022.12.005.

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COMMENT

This study of MEG, which should be the most sensitive method for measuring brain activity, failed to show any statistical difference between tonic, sham, and burst stimulation. It is interesting that EEG and fMRI appears to be a better tool for further study of any differences between SCS modalities.

Marshall Bedder, MD
Augusta, GA, USA