Spatial Filtering of Electroencephalography Reduces Artifacts and Enhances Signals Related to Spinal Cord Stimulation (SCS)

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ABSTRACT

Objectives: How spinal cord stimulation (SCS) in its different modes suppresses pain is poorly understood. Mechanisms of action may reside locally in the spinal cord, but also involve a larger network including subcortical and cortical brain structures. Tonic, burst, and high-frequency modes of SCS can, in principle, entrain distinct temporal activity patterns in this network, but finally have to yield specific effects on pain suppression. Here, we employ high-density electroencephalography (EEG) and recently developed spatial filtering techniques to reduce SCS artifacts and to enhance EEG signals specifically related to neuromodulation by SCS.

Materials and Methods: We recorded high-density resting-state EEGs in patients suffering from pain of various etiologies under different modes of SCS. We established a pipeline for the robust spectral analysis of oscillatory brain activity during SCS, which includes spatial filtering for attenuation of pulse artifacts and enhancement of brain activity potentially modulated by SCS.

Results: In sensor regions responsive to SCS, neuromodulation strongly reduced activity in the theta and low alpha range (6–10 Hz) in all SCS modes. Results were consistent in all patients, and in accordance with thalamocortical dysrhythmia hypothesis of pain. Only in the tonic mode showing paresthesia as side effect, SCS also consistently and strongly reduced high-gamma activity (>84 Hz).

Conclusions: EEG spectral analysis combined with spatial filtering allows for a spatially and temporally specific assessment of SCS-related, neuromodulatory EEG activity, and may help to disentangle therapeutic and side effects of SCS.

Keywords: Mechanisms of action, paresthesia, spinal cord stimulation, thalamocortical dysrhythmia

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INTRODUCTION

Spinal cord stimulation (SCS) can yield excellent clinical outcome in patients suffering from neuropathic pain in terms of pain relief and quality of life (1, 2). Although different modes of stimulation are currently available, all of which can potentially suppress pain, outcomes display high interindividual variability of efficacy and side effects like paresthesia (3). In the absence of valid prognostic markers, SCS in its different modes is either applied in trial and error fashion to the disadvantage of patients in whom SCS fails to show effects, or it is applied only to highly specific etiologies, although other patients might benefit from it. A major obstacle for improving clinical efficacy of SCS and for the optimal selection of stimulation modes in different etiologies is the persistent lack of understanding SCS’s mechanisms of action (2). Pain suppression by SCS is commonly explained by spinal mechanisms on the basis of traditional gate control theory (4). However, as neuromodulatory effects of SCS are apparently more complex involving supraspinal brain structures, research is increasingly focusing on cerebral mechanisms recruited by different stimulation paradigms (3,5,6). In principle, SCS can exert influence on the entire pain matrix (2). As part of the posterior column/medial lemniscal pain matrix (2). As part of the posterior column/medial lemniscal
pathway, A-beta fibers excited by SCS are relayed via medullary nuclei to thalamus and somatosensory cortex (5).

By its rhythmic nature, SCS can modulate brain oscillations, and might therefore also suppress pathological resonances in multiple feedback loops such as thalamocortical loops (7) or even in loops between S1 and spinal cord (8) that have been suggested to contribute to neuropathic pain. Because of its high temporal resolution, electroencephalography (EEG) and magnetoencephalography (MEG) would be ideal techniques to investigate entrainment or desynchronization of brain rhythms by SCS (9). Thus, EEG has recently been used to differentiate cortical effects of high-dose SCS compared to tonic SCS (10).

However, large stimulus artifacts often prevent EEG/MEG analysis of neuromodulatory effects (11). Moreover, the EEG is a complex mixture of activities of various brain sources. In consequence, effects of SCS might easily be confounded with unspecific effects, for example by vigilance changes. The required rigorous experimental controls for these unspecific effects are often difficult to perform with pain patients in a clinical setting. We have therefore developed a pipeline of robust EEG analysis, which largely reduces SCS artifacts in different modes and enhances the somatosensory brain signals potentially modulated by SCS. For this, we use high-density EEG recordings with high sampling rates, reconstruct the different SCS artifacts, and design spatial filters with techniques recently introduced into neuroscience to suppress the artifacts and enhance SCS-related activity (12,13), which largely improves subsequent EEG analysis.

MATERIALS AND METHODS

Patients and SCS

Data were collected from a sample of four chronic pain patients who had received cervical or thoracic epidural spinal cord stimulation for treatment of neuropathic pain due to peripheral and spinal cord injuries (see Table 1 for detailed patient and device information, Fig. 1a). Patients had various etiologies including complex regional pain syndrome (CRPS) and central cord pain due to spinal cavernoma bleeding (for comorbidities, see Table 1). We recorded three of the four patients few days after final implantation of the stimulus generator subsequent to a trial period that proved efficacy of SCS. One of the four patients was recorded two times, in a first session, two days after test implantation with the stimulus generator still being external, and in a second session, one day after final implantation of the stimulus generator, 14 days later. Experiments conformed to the declaration of Helsinki, and were approved by the ethics committee of the Otto-von-Guericke University Magdeburg (135/19).

SCS and EEG Recording

The electroencephalogram (EEG) was recorded from 61 scalp standard positions (Fig. 1b) with ground at electrode AFz and reference at FCz using a Brainamp recording system (Brain Products GmbH, Germany). Additional skin electrodes were placed on face, neck, and arm, in order to measure eye movement, the electrocardiogram, and SCS-related artifacts. SCS patients sat comfortably in a soundproof, electrically shielded recording chamber, always in contact with the experimenter. We recorded resting state EEG with eyes open in blocks of three to five minutes for each SCS mode, and for the condition with SCS switched off. Between blocks, the experimenter selected the stimulation mode for the...
next recording block using the SCS remote control. A block of tonic stimulation (TONIC mode) was recorded in all five sessions. In four sessions the tonic pulse rate was 40 Hz (patients 1, 3, and 4), and in one 80 Hz (patient 2, Table 1). Notably, our analysis was not aiming on detailed differences between specific mode parameters, but on general differences between modes. Blocks of active recharge burst stimulation (BURST mode) with a pulse rate of 200 Hz and a burst rate of 40 Hz, and high-frequency stimulation set to a pulse rate of 1200 Hz (HF mode) were recorded in four sessions in patients 1, 3, and 4. In three sessions (patients 3 and 4) a block of low-frequency stimulation at 2 Hz (LF mode) was recorded to characterize responses to single SCS pulses.刺激强度在所有session中保持在20%低于引起皮质感觉的阈值水平。在所有的session中，我们最后记录了一个装有住电行为的SCS被关掉的setting。我们使用最大的scs bad channels in each session。因为我们知道设置处于同一模式的对应OFF condition。我们通过比较不同的SCS设置在不同模式下的对应OFF condition来收集数据。我们没有告诉研究者哪些设置了SCS模式，尽管他们可能会被完全的遮盲。我们使用5000 Hz的最大可能采样率来记录SCS信号。 

Data Analysis

Using Matlab (The MathWorks, Natick, MA, USA) and the Matlab-based EEGLAB toolbox (12), we set up a robust analysis pipeline for filtering the EEG from SCS artifacts (11) and from confounding unspecific EEG changes, for example, related to vigilance changes during the recording, and for enhancing brain activity modulated by SCS (Fig. 1c). For general artifact rejection, consecutive, nonoverlapping epochs of raw EEG with one second duration were inspected by eye. Epochs containing eye blink artifacts, muscle artifacts, or abnormal signal steps and clippings were excluded from further analysis. We interpolated bad channels after rejection upon visual inspection. Before further analysis, we referenced each EEG channel to a common average reference, and removed signal trends.

Each SCS cycle produced an artifact signal, which allows us to identify the onset of each cycle in each mode. We determined this onset by analyzing the artifact signal either from the EEG channel with the largest pulse artifact or from a bipolar recording with two electrodes placed on the skin of the neck, lateral to the cervical spine. We segmented the artifact signal into consecutive, nonoverlapping epochs of the duration of the SCS interpulse/interburst interval (i.e., 25 ms for TONIC and BURST blocks, and 500 ms for LF blocks). For HF blocks, we spectrally determined the stimulation frequency to be 1204.8 Hz, and used an epoch length of 24.9 ms which exactly includes 30 stimulation cycles. Stimulus-locked pulse artifact waveforms were then reconstructed by averaging artifact signals in a moving window of 24 epochs. This smoothing compensates for slow changes of pulse and burst timing that can arise from sampling errors and clock jitters of the stimulation and recording devices. Reconstructed waveforms consisted of biphasic pulses. The pulse’s onset was determined by marking the time point when the averaged artifact signal crossed a threshold of one standard deviation. We used the time stamp of the positive or negative peak preceded by the longest interpeak interval as marker for SCS cycle onset.
In a second step, we used the SCS cycle onset marker to determine averaged EEG responses during the SCS cycle from $-5$ to $20$ ms relative to cycle onset in TONIC, and BURST, and from $-100$ to $300$ ms in LF mode. In these modes, biphasic pulses of the SCS artifact affected the response up to maximally 7 ms after cycle onset in TONIC and LF modes, and up to 17 ms in the BURST mode (Fig. 2a, artifact intervals marked in light red). In the HF mode, the artifact lasted the entire 24.9 ms interval of the epoch (Fig. 2a, third panel). In turn, we defined a post-artifact response interval from 7 to 20 ms in TONIC mode, and from 7 to 300 ms in LF mode (Fig. 2a, response interval marked in light green). In the other modes, the time interval with only a
small SCS artifact was too short, to reliably estimate a brain response.

In a next step, we used the averaged EEG responses in the artifact and the postartifact interval as target signals to design spatial SCS artifact filters for artifact attenuation, and SCS response filters for enhancing neuromodulatory signals, respectively. Generally, spatial filters consist of weight vectors or matrices, which are multiplied (dot product) with the original multichannel time series, in order to yield a new signal from a weighted sum of all EEG channels. To construct the filter, we used a recently established multivariate technique called joint decorrelation, an extension of principle component analysis (12). It is based on covariance matrices calculated from target and noise signals, and yields a weight matrix for the linear combination of channels that optimizes the defined target signal to noise ratio. The spatial artifact filters (SFA) optimized the signal to noise ratio (SNR) of the averaged EEG signal.

**Figure 3.** Spatial filter for artifact attenuation (SFA) and response enhancement (SFR). a. Examples of topographies of spatial artifact filters for the different SCS modes (sum of five SFA components with the highest SNR) (left three panels), and of a selected response filter component (SFR component with the highest SNR, and the largest SCS-evoked response in its time signal, rightmost panel) from a single recording session. For each mode, the head-map shows the strength of the positive (red colors) or negative (blue colors) contribution of an EEG channels to the artifact for the SFAs or the SCS-evoked response for the SFR. b. The contribution of spatial filter components to the SCS artifacts in the different modes (SFA, left three panels), and the SCS-evoked EEG response (SFR, rightmost panel), quantified as logarithm of the relative signal to noise power ratio (SNR) for the 20 components with the highest SNR. The solid black curves show the grand mean of the log-SNR across recording sessions (n = 5) and the dotted black curves their standard error. The red curve shows the grand mean and standard error of the log-SNR derived from using EEG random samples instead of SCS artifact and response signals as surrogate data for filter construction. The red curve serves as a threshold showing that the components with the highest SNR also had a SNR ratio above noise. c. Time signals of the summed five SFA components with highest SNR are shown for the different SCS modes for each session in the left three panels. Component signals of the SFRs constructed from SCS-evoked response to LF or TONIC stimulation are shown in the rightmost panel. We selected the SFR component with the highest SNR, and the largest SCS-evoked response in its time signal. d. Attenuation and/or enhancement of EEG responses in the artifact and the postartifact response interval, quantified in decibel based on the ratio of the root mean square amplitudes in the intervals before, and after SFA application (left three panels), and before, and after SFR + SFA application (rightmost panel).
response of the artifact interval in each mode, while the spatial response filters (SFR) optimized the SNR of the SCS-evoked single pulse response in the postartifact interval of the TONIC or LF mode (Fig. 2b, that is, the two modes for which SCS artifact was long enough to estimate brain signals, see above). Spatial filters were statistically evaluated by repeating filter construction 500 times with surrogate data randomly resampled from the EEG (12).

Spectral analysis was carried out on artifact free, 1s epochs of transformed EEG signals by applying a 1024 point 5-taper FFT using the chronux Matlab toolbox (14). In order to avoid biasing and double dipping, the spatial artifact filters constructed for each mode were applied all in the same sequence to every signal of a recording session, so that data for all SCS modes were preprocessed identically.

From the SCS response filter components, we selected the one with the highest SNR that showed the smallest artifact residuum and the largest response at latencies longer than seven milliseconds, that is, after the end of the SCS artifact in the TONIC and LF modes used for response filter construction. Spectral analysis was then carried out on the projection of the 61 channel resting state EEG signal on the selected spatial SCS response filter component, or, alternatively, on the EEG channel mean.

As changes in band power might reflect noise-related background changes, we removed aperiodic background activity by fitting a spectral model (15). For statistical analysis, EEG power was averaged in standard frequency bands (2–6, 6–8, 8–12, 12–20, 20–36, 44–76, and 84–130 Hz), and subjected to nonparametric, maximum t value permutation tests, both within, and across subjects, which are applicable to small sample sizes and compensate for multiple testing across frequencies (16).

RESULTS

Spatial Artifact Filtering (SFA) for SCS Artifact Attenuation

Figure 2 shows for each channel the averaged EEG responses evoked during SCS cycles in different modes. EEG responses were dominated by mode-specific SCS artifacts (Fig. 2a, first row). In the TONIC mode (example in Fig. 2a, first panel), and similarly in the LF mode, each single SCS pulse generated a biphasic EEG peak varying in polarity and amplitude across channels. A short train of four or five such biphasic peaks was observed in the BURST mode (Fig. 2a, second panel). In HF mode, the artifact consisted of a fast 1204.8 Hz oscillation (Fig. 2a, third panel).

We constructed spatial artifact filters (SFA, see Methods) from these EEG responses during the artifact intervals (Fig. 2a, artifact intervals marked in light red). Topographies of SFA patterns were highly similar across SCS modes, and showed high correlation of SCS artifacts with the EEG at lateral electrodes close to the neck in all subjects (see example Fig. 3a, left three panels). We statistically evaluated SFA components by randomly sampled surrogate EEG data sets replacing the originally used SCS artifact EEG signals (12). Figure 3b shows the signal to noise ratio (SNR) of the first 20 SFA components. In the grand means for the different SCS

Figure 4. Spatial artifact filters effectively remove SCS artifact pulses from the resting state EEG smoothing spectral SCS artifact peaks. a. Channel mean of single epochs of ongoing EEG in different SCS modes before (blue curves) and after (red curves) attenuating SCS artifacts with a spatial artifact filter (+SFA). Only the first five filter components with the highest SNR for the artifact were used (Fig. 3a). b. Channel mean of power spectra of resting state EEG before (blue curves) and after (red curves) spatial artifact filtering using the SFA. Typical results for different modes in a single session stem from single recording sessions of single patients.
modes, the four to eight components with highest SNR also exceeded the maximum SNR obtained from the surrogate data serving as noise threshold (Fig. 3b, left three panels). In single sessions (not shown), the 3 to 11 components with highest SNR were above noise level. Time signals of filter components reflected the pulse like and oscillatory waveform of the SCS artifacts in the different modes (Figs. 2a and 3c, left three panels).

Sequentially removing the first five SCS artifact components for each SCS mode from the ongoing EEG by applying the SFA largely reduced the SCS artifacts in all modes, with little to no changes in background EEG (Fig. 4a). In the frequency domain, spatial artifact filtering attenuated sharp spectral artifact peaks at multiples of the SCS rate (Fig. 4b). However, spatial artifact filtering also decreased the power at lower frequencies <30 Hz. Low-frequency activity, however, might well be an SCS-related artifact generated by analog hardware filters of the EEG recording system (11). Figure 2b shows the strong attenuation of single pulse SCS artifacts by spatial filtering in the averaged SCS-evoked EEG response compared to Figure 2a. Overall, spatial filter artifacts (SFA) attenuated EEG signal power (rms) in the artifact interval by about 10 to 30 dB in all modes (Fig. 3d). We found no EEG attenuation during the response interval of the TONIC mode, but an attenuation occurred in the response interval of the BURST mode. Apparently burst artifacts still affected the postartifact interval. Therefore, we determined brain responses only from LF and TONIC modes. In the HF mode, there was no artifact-free interval to perform this analysis.

Spatial Filtering of SCS Responses (SFR) for the Enhancement of Neuromodulatory Activity

In a second step, we enhanced SCS-modulated brain activity by constructing a spatial SCS response filter (SFR) using the averaged EEG response to single SCS pulses during the postartifact interval in the TONIC (n = 2) or LF mode (n = 3) (Fig. 2b, response interval marked in light green). We assumed that brain regions showing responses to single SCS pulses in the LF mode were also potentially modulated by SCS. The corresponding SFR pattern topography was consistent with somatosensory activation (see example in Fig. 3a, rightmost panel). In the grand mean, the two SFR components with the highest SNR were also above the maximum SNR obtained from surrogate data (Fig. 3b, rightmost panel). Within single sessions (not shown), we found the first three to five SFR components above maximum surrogate SNR. This indicates that these filter components contained nonrandom, SCS-related activity (12). We selected for each subject and recording session the components showing the smallest artifact residual and the largest response in its time signal. As can be seen in the examples in Figure 3c (rightmost panel), selected SFR components showed deflections at latencies more than seven milliseconds after the SCS pulse, which are unlikely to be artifacts, and apparently reflect SCS-evoked cortical responses. The additional SFR attenuated EEG signal power (rms) during the artifact interval by 25 to 38 dB, and enhanced EEG power during the postartifact response interval by 3 to 5 dB in the TONIC or LF mode (Fig. 3d, rightmost panel). Thus, the SFR further attenuated the SCS artifact, and enhanced the postartifact SCS-evoked EEG response, which then showed polarity inversions as expected from cortical responses to SCS (Fig. 2c).

Spectral Analysis of Spontaneous Activity in Cortical Areas Modulated by SCS

Before spectral analysis, we applied to data from a session the same sequence of spatial artifact filters, one for each mode, in order to avoid introducing differences by spatial filtering itself. After spatial artifact filtering, a spatial response filter was designed from the single pulse responses in the TONIC mode or, if available, the LF mode in each session. We carried out multitaper FFT analysis (14) of the EEG projected onto the SCS response filter components showing in combination the highest SNR, lowest SCS artifact, and largest postartifact EEG response. With this, we enhanced cortical activity evoked by SCS, and therefore activity that was potentially modulated by SCS. To properly analyze changes in oscillatory brain activity, aperiodic background power was removed from the spectra (15). Figure 5a-c shows the power spectra of the spatially filtered (SFA + SFR) resting state EEG in different SCS modes (red curves) in comparison to the corresponding OFF condition in a session (blue curves), as mean across sessions. In all SCS modes, dominant spectral power peaks shifted towards higher frequencies. This led to a reduction of power below 10 Hz and an increase in power above 20 Hz. T-
The TONIC and the HF modes significantly increased high-beta/low-gamma power (20–36 Hz) concomitantly in each individual recording session and on the population level across sessions (Fig. 6a,c, lower row). The BURST mode (Fig. 6b, lower row), increased high-beta/low-gamma power significantly at the population level, but only in three of the four recording sessions. Unique to the TONIC mode (Fig. 6a, lower row), high-gamma power (84–130 Hz) strongly and significantly decreased on the population level and in all five individual sessions. In the other modes, high-gamma power tended to increase. Notably, without applying the spatial response filter (SFR) enhancing SCS-related activity, and instead analyzing the channel mean without spatial response filtering, resulted in a large variance of spectral differences across subjects, and obscured SCS-related spectral effects (Figs. 5d and 6d).

**DISCUSSION**

While SCS has been a clinically effective treatment of neuropathic pain for decades, its mechanisms of action, and in particular its influence on supra-spinal neuronal processing, has remained incompletely understood. Due to its rhythmic nature, interactions of SCS with ongoing rhythms of neural synchrony are likely.
However, gaining insight into such interactions is difficult. The major problem in the electrophysiological analysis of SCS is that SCS-evoked brain responses and SCS-related changes in the ongoing brain activity are difficult to separate from stimulation artifacts and unspecific vigilance effects. However, by spatial filtering we largely reduced SCS artifacts and specifically enhanced SCS-modulated EEG activity revealing distinct and common changes in brain oscillation in different SCS modes. Although our first spatial filter optimized for removing the SCS artifact signal was highly effective in removing SCS artifacts from the ongoing EEG, sometimes small residuals of spectral peaks at SCS-related frequencies and their harmonics remained. By the fact that they persist after spatial filtering, these peaks are less correlated with the reconstructed artifact signal. They could have been generated by hidden artifact sources uncorrelated with our artifact signals or by SCS-evoked brain responses time and phase locked to the SCS cycle, but not fully correlated with the SCS artifact itself. Notably, spatial filtering attenuated the early SCS artifact, without affecting the SCS-evoked response demonstrating that there existed a late response uncorrelated with the artifact. Compared to other methods of electrical stimulus artifact reduction during neuromodulation, our analysis pipeline was highly effective (11). Central topographies of the spatial SCS response filter patterns resembled somatosensory EEG activation (17), and differed from SCS artifact patterns mainly located at lateral temporal and occipital sites.

Spectral analysis after spatial filtering of SCS-related EEG activity revealed distinct and common changes in brain oscillations tonic, burst, and high-frequency modes of SCS. Spectral differences in various frequency bands with respect to modes of SCS have been reported before by a study contrasting an OFF condition with tonic and high-dose SCS (10). In our study, spectral analysis was carried out on spatial filter components calculated as sum of EEG channels weighted by their contribution to SCS responses in the EEG. The spatial filter pattern therefore reflects the topography of the observed spectral effects. However, variation of implantation site and small group size prevented a more detailed spatial analysis of the spectral effects.

The obtained spectral effects were highly consistent across subjects, whereas in the overall EEG of the channel mean, spectral SCS effects were obscured and highly variable across subjects. Thus, application of spatial filters optimized for the enhancement of SCS-evoked responses, also enhanced ongoing EEG activity modulated by SCS.

In the spatially filtered signal components (SFA + SFR), all SCS modes strongly reduced activity in the theta and low alpha range (6–10 Hz) compared to the identically filtered OFF condition, as a common effect. This is consistent with the thalamocortical dysrhythmia (TCD) hypothesis of pain (7). In TCD, thalamic neurons deafferented by local lesions or by enhanced inhibition in the afferent pathways switch into a permanent burst mode generating slow oscillations in this frequency range. Local theta synchronization in turn leads to lateral disinhibition generating “positive” symptoms like pain (7, 9). Recent work has shown that allodynia, which often responds well to SCS, is caused by efferent projections originating from S1 and terminating in the dorsal horn (8). Thus, SCS might modulate neural activity in multiple loops generating pathological brain rhythms (9). Also, mid-frequency activity (20–36 Hz) in the high-beta/low-gamma range tended to increase, which might reflect a regain of normal function in somatosensory areas by SCS. However, as we did not assess pain, we cannot directly attribute observed SCS effects on EEG oscillations to the therapeutic effects of SCS. Only in the TONIC mode, we found a strong decrease of high-gamma activity (84–130 Hz) as a distinct spectral effect. This distinct mode-specific effect could be a correlate of paresthesia associated with this mode. As high-gamma activity has been linked to action potential firing, reduction of high-gamma activity might be due to a suppression of bottom-up input to somatosensory cortex leading to paresthesia (18). Although, evidence of supraspinal SCS mechanisms has grown from studies surmounting technical and ethical hurdles of PET and fMRI imaging with active SCS (19,20), devices are still not approved for common >1.5 T functional magnetic resonance machines, and a number of methodological challenges in imaging central SCS effects on pain remain (21). Thus, nonpainful somatosensory tasks and stimuli also activate the large-scale brain network of the pain matrix (2,22), which might be also detected by the EEG-based connectivity analysis (10). As SCS stimulates somatosensory pathways, observed modulation of the pain matrix might not be specifically related to pain suppression. Nonetheless, normalization of pathological spatiotemporal oscillatory patterns generated in this network might be specifically related to pain and its suppression by SCS (8).

Our analysis pipeline revealed spectral effects of neuromodulation otherwise not seen in the EEG. It was sufficiently robust to show these effects consistently in each patient of our small and diverse sample group. As spatial filtering can be applied time point by time point, it is also well suited for the analysis of more rapid changes in pain, for example, in pain wind-up, or even of paroxysmal pain events. In association with psychophysical and psychophysiological pain assessment, the spatial filtering pipeline can be used to extract signals specifically related to pain processing. In conjunction with source analysis, it can reduce ambiguities, increase robustness of analysis, and enable a specific mapping of neuromodulatory signals onto brain circuits (22). This will create new opportunities for analyzing clinically relevant cortical SCS effects, which can shed light on the neuromodulation of different pain pathways by different SCS modes (23,24).

Authorship Statement

Lars Buentjen, Matthias Deliano, and Petya Vicheva conceived the study. Elena Azañón, Lars Buentjen, Christopher Coutts, Matthias Deliano, Max-Philipp Stenner, and Petya Vicheva designed the study. Lars Buentjen performed SCS surgery on all subjects. Sophie-Antoinette Beccard, Lars Buentjen, Christopher Coutts, Matthias Deliano, and Petya Vicheva acquired the data. Matthias Deliano and Petya Vicheva analyzed the data. Lars Buentjen, Bankim Subhash Chander, Matthias Deliano, and Max-Philipp Stenner drafted the manuscript. All authors revised the manuscript for critically important intellectual content.

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COMMENT

The paper by Buentjen and co-workers is a very good manuscript, very well written. The methods are sound and the idea is completely novel for the huge field of spinal cord stimulation. The paper investigated a hot topic recently arising in the current literature: the role of brain modulation induced by SCS in humans. In particular, a growing body of literature has recently shown that SCS, especially when delivered as beta-burst stimulation, modulates both spinal and supra-spinal dynamics. Although the exact mechanisms of action and the underlying pathways still remain elusive, both fMRI and neurophysiological studies have confirmed these findings.

The modulation of cortical beta oscillations is interesting. In particular, their modulation, preferentially induced by burst stimulation, may suggest the possibility to interfere with several phenomena, possibly shortening reaction times for voluntary movements, improving at the same time both motor withdrawal and nociceptive processing at a spinal level.

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