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High-Frequency Spinal Cord Stimulation Reorganizes Frequency-Dependent Cortical Modules of Tibial Nerve Stimulation-Evoked Activity in Sheep

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ABSTRACT:

Spinal cord stimulation (SCS) is widely used for the treatment of chronic pain, while newer paradigms, such as high-frequency SCS (hSCS), provide improved efficacy with reduced paresthesia-related side effects. Although SCS has traditionally been thought to act primarily through spinal mechanisms, increasing evidence indicates that supraspinal networks also contribute to therapeutic effects. Here, we investigated how hSCS alters modular architecture of large-scale cortical functional network (CFN) using 96-channel electrocorticography (ECoG) recordings from anesthetized sheep ($n = 4$) spanning the somatosensory and association cortices. Frequency-specific functional connectivity matrices were constructed separately for low-frequency (4–12 Hz) and high-frequency (70–150 Hz) activity during the pre-stimulation (TNS_0) and post-stimulation (TNS_1) conditions. Graph-theoretical unsupervised modularity approach was used to characterize frequency-dependent changes in the modular CFN architecture. Across animals, CFNs consistently segregated into distinct functional modules that closely corresponded to the anatomical boundaries between the somatosensory and association cortices, despite the absence of anatomical constraints during clustering. The hSCS induced robust frequency-dependent and region-specific reorganization of these modules, with substantially greater modulation in the high-frequency band than in the low-frequency band. High-frequency networks exhibited stronger intermodular correlations, greater trial-to-trial variability, and more pronounced condition-dependent reorganization, whereas low-frequency networks remained relatively stable. In several animals, somatosensory and association cortices exhibit opposing patterns of modulation, suggesting reciprocal reorganization of cortical communication following hSCS. Together, these findings suggest that, in the ovine CFN, functional boundaries closely follow structural boundaries. Furthermore, hSCS can reshape modular architecture of large-scale CFNs through frequency-dependent reorganization, providing new insights into the supraspinal mechanisms underlying hSCS.

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1. INTRODUCTION:

Although traditional paresthesia-based spinal cord stimulation (P-SCS) has evolved through approaches such as dorsal root ganglion stimulation (DRG-S), burst SCS (B-SCS), and high-frequency SCS (hSCS) [1–4], the mechanisms by which these paradigms influence large-scale brain network organization remain incompletely understood [5–9]. Despite the fact that pain perception and modulation ultimately emerge from distributed cortical and subcortical circuits, traditional theories of SCS have largely emphasized spinal mechanisms, particularly segmental gating within the dorsal horn[10], supported by extensive experimental evidence demonstrating modulation of dorsal horn neuronal activity and ascending nociceptive transmission[11]. However, the supraspinal effects of paresthesia-free hSCS have not yet been thoroughly investigated. In particular, the effects of hSCS on distributed cortical network dynamics have received limited attention.

Neural oscillations are central to coordinating neural activity both locally and globally in the brain [12,13]. High-frequency oscillations are commonly associated with local sensory processing, whereas low-frequency rhythms are thought to facilitate long-range integration between cortical regions by coordinating and modulating higher-frequency activity [14–18]. Previous studies have shown that hSCS modulates cortical oscillatory activity [19–23], including changes in high-gamma (70-150 Hz) activity and low-frequency (4-30 Hz) dynamics. Specifically, one the same sheep used in this study, we have shown that hSCS modulates theta-gamma coupling while suppressing the amplitude of high-gamma oscillations [22,23]. However, how these oscillatory changes

translate into alterations in large-scale cortical functional network (CFN) architecture and interregional communication remains unclear.

To address this question, we employed a graph theoretical modularity approach to characterize the community structure and dynamic organization of brain networks [24,25], which quantifies how strongly nodes (e.g., ECoG recording sites) cluster into internally coherent groups, thus providing a robust framework to assess functional segregation and integration in cortical systems [26,27]. Importantly, these approaches provide standardized metrics that can be compared across species, methodologies, and clinical neuromodulation paradigms.

We hypothesized that hSCS would induce frequency-dependent reorganization of CFN, with more pronounced modulation in association cortices involved in large-scale integration than in primary somatosensory regions. This prediction is supported by anatomical evidence showing that association cortices are more densely interconnected and dynamically integrated than primary sensory areas [28–30].

To test this hypothesis, we computed frequency-specific functional connectivity matrices from electrocorticographic (ECoG) recordings obtained in sheep during tibial nerve stimulation, before and after hSCS. Modularity analysis were performed directly at the sensor level to avoid confounding factors associated with source reconstruction. By comparing CFN organization across stimulation conditions, we aimed to determine how hSCS reshapes the functional modularity, intermodular interactions, and dynamic CFN states associated with sensory processing.

2. METHODS:

2.1 Ethics Approval:

Four adult sheep, each weighing 58–71 kg, were used in this study. All procedures were reviewed and approved by the University Animal Care and Use Committee (IACUC, #0902039) and complied with the ARRIVE guidelines. All experiments were performed in accordance with relevant guidelines and regulations.

2.2 Surgical Procedure and Anesthesia Protocol:

The animals were anesthetized with inhaled isoflurane via endotracheal intubation. Prior to making the skin incisions, 10–20 cc of 2% lidocaine was injected locally. Figure 1i illustrates the nociceptive pathway in sheep, whereas Figure 1ii depicts the primary somatosensory cortex and adjacent association areas. In sheep, these higher-order association areas are positioned next to the primary somatosensory cortex and are believed to maintain dense reciprocal connections, similar to other mammalian species [28–30].

A longitudinal incision was made along the posterior side of the hind limb anterior and proximal to the calcaneus to expose the left tibial nerve. Two EMG needle electrodes were inserted directly into the nerves. A right-sided hemicraniectomy was then performed, followed by dural opening (Fig. 1iii). A 96-contact platinum-iridium subdural grid (Ad-Tech Medical Instruments, Racine, WI, USA) was placed over the right cerebral hemisphere, covering both primary somatosensory and adjacent association cortices (Fig. 1iv). The grid had contacts of 1.4 mm diameter with 3.0 mm inter-contact spacing. Association areas are thought to integrate sensory inputs from multiple modalities for higher-level processing [28].

155 Additionally, a four-contact platinum-iridium reference electrode was implanted in the
156 subgaleal space over the frontal bone. To expose the spinal cord, laminectomy spanning
157 T7 to T10 was performed. The dura was opened under a surgical microscope and a
158 custom-made bipolar neurostimulation probe (Fig. 1v–vii) was positioned over the dorsal
159 spinal cord at the T11 level using a micromanipulator for stability [19,31]. Hemostasis was
160 maintained throughout the procedure and the surgical field was irrigated with sterile
161 saline.

162 Thirty minutes before data acquisition, anesthesia was transitioned to a continuous
163 intravenous infusion of light Propofol (0.4 mg/kg/h), and inhaled Isoflurane was
164 discontinued. Anesthetic depth was monitored regularly using corneal reflex testing. The
165 core body temperature was continuously monitored via a rectal probe and maintained
166 within physiological limits using warming pads and heated intravenous fluids. Vital signs,
167 including blood pressure, heart rate, core temperature, end-tidal isoflurane concentration,
168 and oxygen saturation, were continuously recorded throughout surgery and data
169 collection. After the experiments, animals were euthanized using intravenous
170 pentobarbital (120 mg/kg).

171 **2.3 Electrical Stimulation and Experimental Design:**

172 Following discontinuation of inhaled anesthesia, all animals underwent a 30-minute
173 stabilization period before recording began. On average, each sheep underwent
174 approximately 13 ± 2 hours of combined surgical and experimental procedures. Each
175 animal was subjected to three sequential recording conditions (Fig. 1viii): (1) tibial nerve
176 stimulation before spinal cord stimulation (TNS₀); (2) simultaneous tibial nerve stimulation
177 and high-frequency spinal cord stimulation (hSCS); and (3) tibial nerve stimulation

following hSCS (TNS_1). TNS_0 and TNS_1 were compared to assess hSCS-induced changes in cortical network organization.

2.4 Tibial Nerve Stimulation (TNS):

TNS was delivered using a grass constant-current stimulator at 0.5 Hz (one stimulus every 2 s) with a pulse width of 200 μ s. Stimulation intensity was set above the motor threshold to reliably evoke cortical somatosensory responses. Although the pain threshold was not directly quantified, the stimulation intensity was likely sufficient to recruit sensory afferents and may have engaged in nociceptive/spinothalamic pathways depending on the effective stimulation intensity. This stimulation paradigm generated robust somatosensory evoked potentials (SSEPs) and associated oscillatory responses, enabling standardized comparisons of cortical activity before and after hSCS, while minimizing the overlap between consecutive evoked responses.

2.5 High-Frequency Spinal Cord Stimulation (hSCS):

Under direct microscopic visualization, a custom bipolar neurostimulation probe (10.5 k Ω impedance at 20 Hz) was positioned on the pial surface of the spinal cord (Fig. 1v). Charge-balanced square pulses (122 μ s pulse duration) were delivered using an IZ-2 stimulator (Tucker-Davis Technologies, Alachua, FL, USA) (Fig. 1v–vi). Bipolar stimulation was applied, with the cathode positioned rostrally relative to the longitudinal axis of the spinal cord. The probe consisted of two spherical contacts (1.0 mm diameter) separated by 2.0 mm. hSCS were delivered continuously for 15 min at a stimulation frequency of 8.196 kHz. The experimental timeline is shown in Figure 1vii.

2.6 Electrocorticography (ECoG):

ECoG signals were recorded from the 96-contact subdural grid (Fig. 1ii) using a Tucker-Davis Technologies multichannel acquisition system (RZ-2 and PZ-2, Alachua, FL, USA) sampled at 5 kHz. The duration of TNS recordings differed across sheep, resulting in variability in the total trial counts between animals. However, within each animal, the pre- (TNS₀) and post-hSCS (TNS₁) trial numbers were closely matched (sheep 1:448/450; sheep 2:299/298; sheep 3:148/145; sheep 4:149/149 trials, pre and post, respectively). The duration of hSCS exposure also varied across the animals (sheep 1,15 min; sheep 2,15 min; sheep 3,5 min; sheep 4,10 min). Importantly, all TNS-evoked epochs were 1s in duration, ensuring consistency in epoch length and time-resolved analyses across the animals.

2.7 Signal Processing:

ECoG data were processed offline using custom MATLAB (2023a) scripts. The power line noise (60 Hz and harmonics) was removed using an adaptive notch filter (59.5–60.5 Hz). Trials with amplitudes greater than 10 standard deviations from the block mean were discarded. Evoked potentials were analyzed using epochs extending from 50 ms before to 400 ms after TNS onset.

2.8 Functional Connectivity Analysis:

Functional connectivity between the ECoG channels was quantified using magnitude-squared coherence. The pre-stimulation and post-stimulation trials were first concatenated, and trials containing only zero values across all channels and time points were excluded from further analysis. For each remaining trial, coherence was calculated between all pairs of channels using the MATLAB '*mscohere*' function on each trial,

corresponding to approximately 1 s of recording at a sampling rate of 4069 Hz. This procedure generates trial-specific weighted adjacency matrices that represent pairwise functional connectivity. Connectivity was evaluated separately within the low-frequency (4–12 Hz) and high-frequency (70–150 Hz) bands by averaging coherence values across the corresponding frequency ranges. The resulting connectivity matrices were symmetrized, and self-connections were removed by setting the diagonal elements to zero. Channels identified as noisy or excluded from a given animal were removed from the analysis by setting the corresponding rows and columns to zero.

For each frequency band, trial-specific adjacency matrices were averaged across the trials to obtain a representative weighted connectivity matrix. These matrices served as the adjacency matrices (A_{ij}) used in all subsequent graph-theoretical analyses, where each element A_{ij} represents the coherence-derived functional connectivity (edge weight) between ECoG channels i and j , and $A_{ii} = 0$ indicating the absence of self-connections. Subsequently, these adjacency matrices were used for modularity estimation and subnetwork identification.

2.9 Modularity Analysis and Subnetwork Identification

To characterize the modular organization of the CFNs, we employed a combination of graph-theoretical unsupervised community detection [24] and supervised optimization procedures [32]. In the first step, the community structure was identified using an eigenvector spectral modularity method. The modularity matrix is defined as

$$B_{ij} = A_{ij} - \gamma \frac{k_i k_j}{2m}, \quad (i)$$

Where (A_{ij}) is the adjacency matrix; (k_i) and (k_j) are the node strengths; m is the total edge weight; and (γ) is the resolution parameter. The modularity of a partition is given by

$$Q = 1/2m \sum_{(i,j)} (A_{ij} - \gamma(k_i k_j)/2m) \delta(c_i, c_j) \quad (ii)$$

where $\delta(c_i, c_j) = 1$ if nodes (i) and (j) belong to the same community and 0 otherwise.

Modularity matrix (B) was eigen-decomposed, and its largest positive eigenvalue was used to bipartition the network by assigning nodes according to the sign of their corresponding eigenvector elements. This procedure was then applied recursively to each resulting subnetwork, and further subdivision was accepted only when it produced a positive increase in the modularity $\Delta Q > 0$. However, a key parameter in this procedure is the modularity resolution parameter (γ) , which determines the scale at which modules are detected. Lower values of this parameter tend to detect larger modules with fewer subdivisions, whereas higher γ values result in smaller and more numerous subnetworks, owing to stricter connectivity requirements.

To determine the optimal γ value, we implemented a supervised optimization procedure based on the modularity ratio (MR) metric. For each candidate γ value, The network was partitioned into modules for each candidate γ value and the internal connectivity of each module was quantified. This value was then compared against a null model generated through randomization while preserving the average connectivity weights and correct distribution of the original network. The MR was computed as the ratio between the average intra-module connectivity in the empirical network and that in the randomized network [25,32]:

$$MR = \frac{\text{Mean intra-module connectivity in the empirical network}}{\text{Mean intra-module connectivity in the randomized network}} \quad (iii)$$

A greater MR indicated that the detected modules exhibited stronger internal connectivity than expected by chance.

This procedure was repeated across all detected modules, and the MR values were averaged to obtain the global MR for each γ . The modularity parameter was then systematically increased until the network was fragmented into isolated nodes. Optimal γ was defined as the value that maximized the global MR while avoiding excessive fragmentation of the network.

Once the optimal modular structure was identified, the resulting module assignments were retained for subsequent analyses to ensure consistency across comparisons. This framework allows for data-driven and statistically grounded identification of subnetworks while minimizing the influence of spurious modular structures arising from global connectivity patterns.

To perform the unsupervised modularity analysis, we used the Brain Connectivity Toolbox [33] and to assess the supervised modularity, which we used in MATLAB 2019b (publicly available at <https://github.com/AHGHaderi/Amir-Hossein-Ghaderi/commit/df636b2105e578a8969ffa88856e54f3267a40a7>).

2.9 Statistical Analysis

Statistical analyses were performed using the MATLAB software. For each animal, modularity values obtained before and after high-frequency spinal cord stimulation (hSCS) were compared separately for each cortical module identified by the community

detection algorithm within the low- and high-frequency networks. Observations with missing values were excluded from analysis.

For each identified module, pre- and post-stimulation modularity values were compared using a two-sided Wilcoxon rank-sum (Mann–Whitney U) test implemented with the MATLAB ‘ranksum’ function. Statistical comparisons were performed independently for each module, within each frequency band.

To account for multiple comparisons, Bonferroni correction was applied separately for each animal and frequency band by adjusting the P-values according to the total number of modules identified in that network. Corrected P values greater than 1 were set to 1. Statistical significance was defined as $P < 0.05$, $P < 0.01$, and $P < 0.001$ after Bonferroni correction. Significance annotations shown in the figures correspond to Bonferroni-corrected P values.

3. RESULTS:

To investigate the effects of hSCS on CFN dynamics, we performed modularity analysis on ECoG recordings obtained from the somatosensory and association cortices of four sheep. Modularity ratios (MR) were computed during baseline tibial nerve stimulation (TNS_0) and following hSCS (TNS_1) for both low- and high-frequency CFNs. By examining the modular structure of cortical connectivity, we aimed to determine how hSCS alters the large-scale functional organization across cortical regions and frequency bands. Across animals, hSCS induced frequency-dependent changes in cortical modularity that differed between the cortical regions and frequency bands. In general, the modulation was more pronounced in high-frequency networks, whereas low-frequency networks remained

relatively stable. Additionally, in several animals, opposite patterns of modulation were observed between the somatosensory and association cortices, suggesting that hSCS differentially reorganizes interconnected CFNs involved in sensory and higher-order associative processing.

3.1 Modularity Analysis Reveals Frequency-Robust Anatomical Segregation:

To examine the relationship between functional network organization and cortical anatomy, we analyzed ECoG data from sheep 1, in which electrode coverage spanned both somatosensory and association cortices. **Figure 2A** (left) illustrates the anatomical layout of the implanted grid, with the red outline demarcating the boundary between the somatosensory cortex (inside the boundary) and association cortex (outside the boundary). A modularity detection algorithm (see Methods) was applied to functional connectivity matrices derived separately from low- and high-frequency activity, with connectivity estimates averaged across the TNS₀ and TNS₁ conditions.

The low-frequency modularity map (**Fig. 2A, middle**) shows four spatially distinct modules. Modules 1 and 2 were primarily localized within the association cortex, whereas Modules 3 and 4 corresponded closely to the somatosensory cortex, demonstrating strong agreement with the known anatomical boundary. These module maps were generated using a network partition that maximized the modularity ratio MR (**Supplementary Figure 1**). Importantly, this functional parcellation emerged without incorporating anatomical constraints into the clustering procedure, indicating that modularity analysis recovered physiologically meaningful cortical organization in a fully data-driven manner.

The high-frequency modularity map (**Fig. 2A, right**) also identified four modules with similar overall spatial organization despite minor differences in node composition. These findings suggest that the modular structure was largely preserved across the frequency bands and reflected the underlying anatomical segregation of the cortical regions.

Similar analyses in Sheep 2–4 (**Fig. 2B–2D**) further validated this approach. Sheep 2 exhibited six modules in the low-frequency band and five modules in the high-frequency band. Sheep 3 demonstrated four modules in both frequency bands, and sheep 4 showed five low-frequency and three high-frequency modules. Despite inter-animal variability in module number and detailed configuration, the resulting modular organization consistently aligned with the anatomical separation between the somatosensory and association cortices inferred from electrode placement and cortical landmarks. Notably, these modularity maps closely resembled the modulation index maps ($TNS_1 - TNS_0$) obtained from the same sheep [23].

Together, these findings demonstrate that functional modularity derived from ECoG network analysis robustly captures anatomically meaningful cortical subdivisions across animals and frequency bands. Across all sheep, the modularity approach reliably parcellated CFNs in a manner consistent with the known cortical organization, highlighting the validity of this approach for data-driven cortical mapping.

3.2 Modularity: Pre vs. Post in high and low bands

Having established that the detected modules corresponded closely to anatomically meaningful cortical subdivisions, we examined how hSCS altered module-specific

modularity. Specifically, we compared the modularity ratio (MR) between TNS_0 and TNS_1 for all identified modules in both the low- and high-frequency bands (**Fig. 3**).

In Sheep 1 (**Fig. 3A**), low-frequency modularity analysis (**Fig. 3A, left**) revealed significant increases in Modules 1 and 2, both of which localized predominantly within the association cortex, whereas Modules 3 and 4, localized primarily within the somatosensory cortex, showed no significant differences between TNS_0 and TNS_1 . In the high-frequency band (**Fig. 3A, right**), Modules 2 and 3 demonstrated significant increases in modularity following hSCS, whereas Module 4 showed a significant decrease, and Module 1 remained unchanged.

In Sheep 2 (**Fig. 3B, left**), low-frequency modularity analysis revealed no significant differences between TNS_0 and TNS_1 across the identified modules, indicating relatively stable low-frequency modular organization following hSCS. In contrast, the high-frequency modularity analysis (**Fig. 3B, right**) demonstrated significant changes in the selected modules. Module 3 exhibited a significant increase in modularity following hSCS, whereas Module 5 showed a significant decrease. The remaining modules did not differ significantly between the TNS_0 and TNS_1 . Based on the anatomical distribution of these modules, shown in **Figure 2B**, increases were observed primarily within the somatosensory cortex, whereas decreases were observed primarily within the association cortex modules.

In Sheep 3 (**Fig. 3C, left**), low-frequency modularity analysis revealed a significant decrease in module 3, localized within the somatosensory cortex, whereas the remaining modules showed no significant differences between TNS_0 and TNS_1 . In the high-

frequency band (**Fig. 3C, right**), all the identified modules demonstrated significant changes following hSCS. Association cortex modules exhibited increased modularity, whereas somatosensory-associated modules both increased and decreased, depending on their composition.

In Sheep 4 (**Fig. 3D, left**), low-frequency modularity analysis revealed a significant change only in Module 3, spanning both the association and somatosensory cortices, whereas the remaining modules showed no significant differences between the TNS₀ and TNS₁ conditions. In contrast, high-frequency modularity analysis (**Fig. 3D, right**) demonstrated a significant increase in **Module 3** localized primarily within the somatosensory cortex following hSCS. All corrected p values are shown in **Supplementary Figure 2** and correspond to the significance levels indicated by asterisks ($p < 0.05$, $*p < 0.01$, $p < 0.001$).

Taken together, these findings demonstrate that hSCS induces frequency-dependent and region-specific reorganization of cortical modularity. Modulation was generally more pronounced in the high-frequency modules, whereas the low-frequency modules remained comparatively stable. Across multiple animals, the association and somatosensory cortices exhibited opposing patterns of modulation, with increases in modularity within one region often accompanied by decreases in the other, suggesting differential effects of hSCS on interconnected cortical modules. These findings suggest that hSCS alters the balance of communication within distributed CFNs rather than producing a uniform reorganization of cortical connectivity.

4. Discussion

Together with our previous demonstrations [22,23] that hSCS suppresses cortical high-gamma activity and modulates theta-gamma coupling, the present findings indicate that hSCS additionally reorganizes the large-scale modular architecture through which these oscillatory signals are coordinated. Using high-density ECoG recordings combined with unsupervised modularity analysis, we found that cortical subnetworks were consistently segregated according to anatomical boundaries between the somatosensory and association cortices across animals and frequency bands. hSCS subsequently altered the strength and organization of these modules, with the effects being substantially more pronounced in high-frequency networks than in low-frequency networks.

4.1 hSCS Reshapes Cortical Network Modularity

A major finding of the present study was that unsupervised modularity analysis reliably recovered an anatomically meaningful cortical organization. Across animals, the identified modules closely aligned with the known separation between the somatosensory and association cortices, despite the absence of anatomical priors during clustering [26,33,34]. Importantly, this organization was largely preserved across both the low- and high-frequency networks. These findings suggest that intrinsic cortical connectivity imposes stable constraints on functional network organization that remains detectable across oscillatory regimes [26,34]. Although the number and precise configuration of modules varied somewhat across animals, the broader segregation between somatosensory and association regions remained consistent. Modularity is widely regarded as a fundamental principle of efficient brain organization because it balances functional segregation with network integration, allowing specialized cortical subnetworks

to process information locally, while maintaining coordinated communication across distributed brain regions [33–35]. Consequently, changes in modular organization reflect alterations in how information is integrated and exchanged across cortical networks rather than changes in activity within isolated regions [35–37]. The frequency-dependent modulation of modularity observed following hSCS suggests that spinal stimulation reshapes large-scale cortical communication, while preserving the underlying anatomical framework.

The preservation of this anatomical organization across frequency bands is notable, because low- and high-frequency oscillations are thought to support partially distinct physiological processes [12,13,15]. Despite these differences, both frequency bands retained modular structures that recapitulated the cortical anatomy, suggesting that large-scale anatomical scaffolding strongly constrains cortical communication independent of oscillatory frequency [33,34]. This observation further supports the idea that functional modularity is not random or purely state-dependent but instead reflects the underlying anatomical and physiological organization [26,33].

4.2 Preferential Modulation of High-Frequency Cortical Networks

While the overall spatial organization of the modules remained relatively stable, hSCS significantly altered modularity strength across stimulation conditions. These effects were considerably more pronounced in high-frequency networks, whereas low-frequency modularity often remained relatively stable after stimulation. High-frequency modules demonstrated robust increases or decreases in modularity across animals and cortical regions, indicating that hSCS preferentially influenced local cortical processing dynamics

rather than globally reorganizing slower, large-scale networks. Because high-frequency oscillations are closely linked to local neuronal population activity and cortical information processing, preferential modulation of these networks suggests that hSCS primarily alters the organization of local cortical computations, while leaving the broader low-frequency integration intact [12,15,35,38,39].

The preferential modulation of high-frequency networks may reflect the sensitivity of local cortical processing to altered ascending sensory inputs following hSCS. High frequency activity is closely associated with local neuronal population activity and cortical excitability, making it particularly responsive to neuromodulatory interventions [20,21,38,39]. In contrast, the relative stability of low-frequency modular organization suggests that a slower integrative network architecture may remain comparatively preserved despite substantial changes in local cortical communication [12,13].

4.3 Differential Reorganization of Somatosensory and Association Cortices

Another striking finding was that the somatosensory and association cortices frequently exhibited opposing patterns of modulation following hSCS. In several animals, modules localized primarily within the association cortex increased in modularity, whereas somatosensory modules decreased, whereas other animals demonstrated the reverse pattern. These reciprocal effects suggest that hSCS does not simply produce uniform increases or decreases in cortical synchrony but instead dynamically redistributes communication across interconnected cortical systems. Such a reorganization may reflect a shifting balance between sensory-driven processing and higher-order associative integration.

Association cortices are densely interconnected and support integrative processing across distributed cortical systems [12,40]. Therefore, increased modularity within these regions may reflect enhanced internal coordination or segregation of higher-order processing networks following hSCS. Conversely, reductions in somatosensory modularity may indicate the redistribution of information flow across broader cortical systems. Together, these findings suggest that hSCS may reshape cortical processing by reweighting interactions between sensory and associative networks, rather than independently altering isolated cortical regions.

4.4 Supraspinal Mechanisms of High-Frequency Spinal Cord Stimulation

These observations are relevant to the growing recognition that spinal cord stimulation exerts substantial supraspinal effects [1–3,41]. Traditional theories of SCS have largely emphasized spinal gating mechanisms within the dorsal horn [10]. However, increasing evidence suggests that neuromodulation also alters thalamic, cortical, and large-scale network activity [1–3,42]. Within the cortex, these supraspinal effects have been associated with changes in neuronal excitability, cortical oscillatory activity, and functional communication between distributed cortical regions, indicating that SCS engages widespread cortical processing beyond the initial modulation of ascending sensory pathways [3,43–46]. Recent human functional MRI studies further demonstrate that SCS produces parameter-dependent modulation of supraspinal networks, including the sensorimotor cortex, thalamus, salience network, and default mode network, while simultaneously altering the connectivity between pain-processing regions [47]. These findings indicate that distinct stimulation paradigms recruit different large-scale cortical

circuits that are associated with pain perception and modulation. Our electrophysiological findings extend these observations by demonstrating that hSCS reorganizes cortical functional connectivity and theta-gamma interactions with millisecond temporal resolution [22,23], providing a potential neurophysiological substrate for large-scale BOLD network changes observed with functional MRI. The present findings extend these observations by showing that hSCS reorganizes the modular architecture of CFNs in a frequency-dependent manner.

Together, these studies suggest that hSCS influence cortical processing at multiple hierarchical levels, ranging from local sensory responses and oscillatory interactions to large-scale functional network organization. Such a distributed cortical reorganization may contribute to the therapeutic effects of hSCS.

4.5 Limitations and Future Directions

Despite the overall consistency of the findings, considerable inter-animal variability was observed in the magnitude and direction of the modularity changes. Differences in cortical anatomy, electrode positioning, stimulation duration, baseline cortical state, and anesthetic effects may have contributed to this heterogeneity [48,49]. However, the presence of variability did not diminish the broader pattern of findings. Rather, it emphasizes the dynamic and state-dependent nature of the cortical responses to neuromodulation. Similar variability has been reported across both animal and human neuromodulation studies, and may ultimately prove important for understanding differential therapeutic responsiveness [2,3].

This study had several limitations. First, recordings were obtained under anesthesia, which likely influenced oscillatory activity and cortical connectivity patterns [48,49]. Second, the sample size was limited to four animals, restricting statistical generalization. Third, the stimulation duration differed across animals and may have contributed to the variability in the network responses. Finally, coherence-based connectivity measures may be influenced by common reference effects and volume conduction [50,51], although the strong anatomical specificity of the resulting modules contradicts purely artifactual explanations.

Future studies should examine how these network effects evolve in awake and behaving preparations and determine whether specific modularity signatures correlate with behavioral or nociceptive outcomes [52]. Additional approaches examining directed connectivity, temporal dynamics, and cross-frequency interactions may further clarify how hSCS reshape communication across cortical hierarchies.

5. Conclusion

In conclusion, the present findings demonstrate that hSCS induces dynamic and frequency-dependent reorganization of cortical modularity while preserving the broader anatomical structure of the cortical networks. Functional modules consistently recapitulated anatomical boundaries between somatosensory and association cortices, and hSCS preferentially altered high-frequency network organization with region-specific and often reciprocal effects across cortical systems. Together with our previous demonstrations of hSCS-induced modulation of cortical high-gamma activity and theta-gamma coupling [22,23], these findings indicate that hSCS reorganizes cortical

527 processing across multiple hierarchical scales, from local oscillatory dynamics to a large-
528 scale functional network architecture.

529 **Additional information:** The authors have no competing interests as defined by Nature
530 Research, or other interests that might be perceived to influence the results and/or
531 discussion reported in this paper

532 **Data Availability Statement:** The datasets generated and/or analyzed during the current
533 study are available from the corresponding author, Vishal Bharmuria (VB), upon
534 reasonable request.

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655

656 **Author contributions:**

657 VB and AG contributed equally to this work and share first authorship. VB: Methodology,
658 formal analysis, validation, investigation, visualization, data curation, writing – original

659 draft, writing – review, and editing. HO: methodology, conceptualization, data curation,
660 investigation, validation, formal analysis, writing – review and editing, and project
661 administration. YB: Validation, investigation, writing, review, and editing. NS:
662 Visualization, validation, formal analysis, and investigation. AG: investigation, formal
663 analysis, visualization, writing, review, and editing. YYB: Visualization and formal
664 analysis. KJ: Visualization, writing, reviewing, and editing. AS: Validation, writing, review,
665 and editing. ALG: Writing, review, and editing. HK: conceptualization, methodology,
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667 review and editing, and project administration. CS: Validation, writing, review, and editing.
668 BD: validation, writing, review, and editing. AML: validation, writing, review, and editing.
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670 validation, supervision, funding acquisition, writing – review and editing, and project
671 administration. OF: conceptualization, methodology, data curation, investigation,
672 supervision, funding acquisition, writing – review and editing, and project administration.

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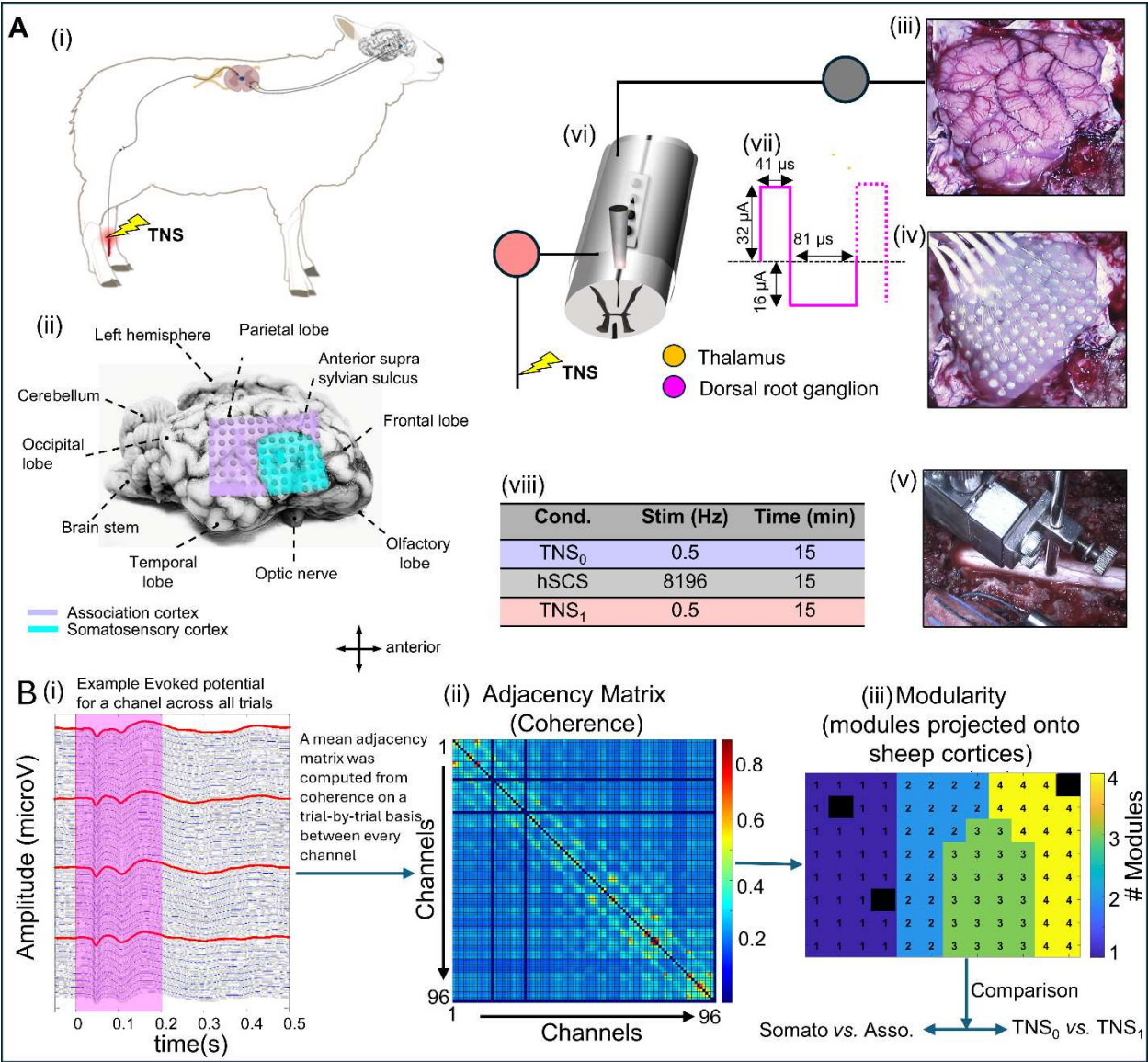


Figure 1. Experimental configuration and analysis workflow. (A) Recording and stimulation setup during tibial nerve stimulation (TNS). (i) Conceptual schematic of the mammalian somatosensory pathway, depicting signal transmission from the peripheral nerve to higher-order cortical regions. (ii) Dorsal view of the sheep brain showing the placement of a 96-contact subdural ECoG grid covering primary somatosensory cortex (cyan) and adjacent association cortex (purple). (iii) Intraoperative photographs of the exposed cortex before (top) and after (bottom) grid placement in Sheep 1, illustrating anatomical landmarks. (iv) Close-up view of the implanted ECoG electrode array. (v) Custom high-frequency spinal cord stimulation (hSCS) probe used for neuromodulation. (v-vi) Stimulation parameters applied during hSCS, including pulse frequency, pulse width, and current amplitude. (vii) Experimental timeline showing sequential recording blocks: baseline TNS (TNS_0), combined TNS + hSCS, and post-stimulation TNS (TNS_1).

(B) Network analysis pipeline. (i) Example somatosensory evoked potential aligned to TNS onset (time 0) from a representative channel and animal during TNS₀. (ii) Mean adjacency matrix computed by averaging coherence across trials. (iii) Community structure identified via modularity analysis, illustrating four detected network modules

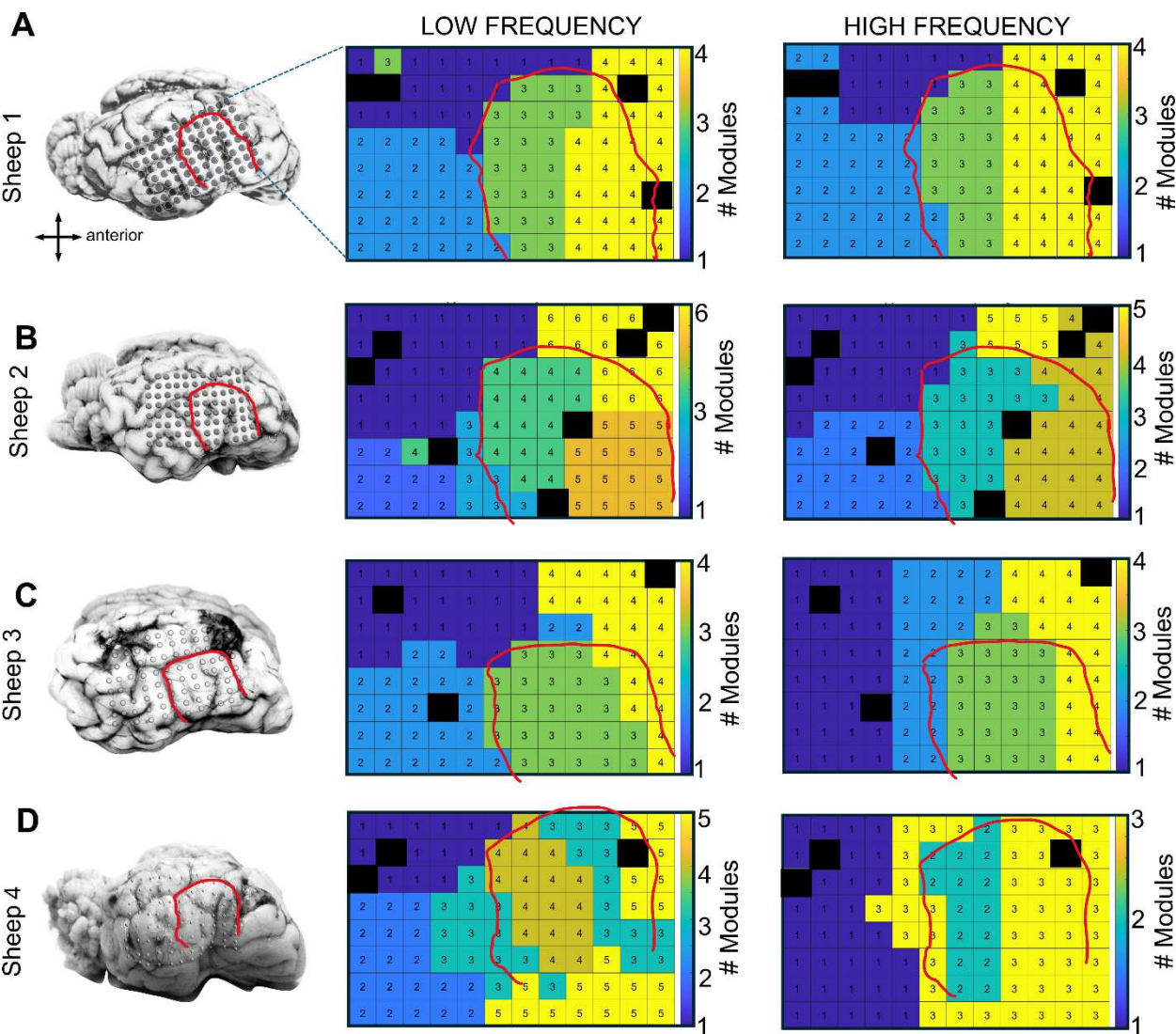


Figure 2. Frequency-resolved functional modularity recapitulates cortical anatomy. Unsupervised modularity analysis of ECoG functional connectivity reveals spatially organized network modules that align with known anatomical boundaries between somatosensory and association cortices. In Sheep 1 (A), low- and high-frequency networks identify distinct modules that closely match the somatosensory–association cortex division (red outline), despite no anatomical constraints in the analysis. Similar frequency-dependent yet anatomically consistent modular organization is observed across Sheep 2–4 (B–D), demonstrating robust, data-driven parcellation of cortical structure across animals. The black squares indicate the eliminated channels.

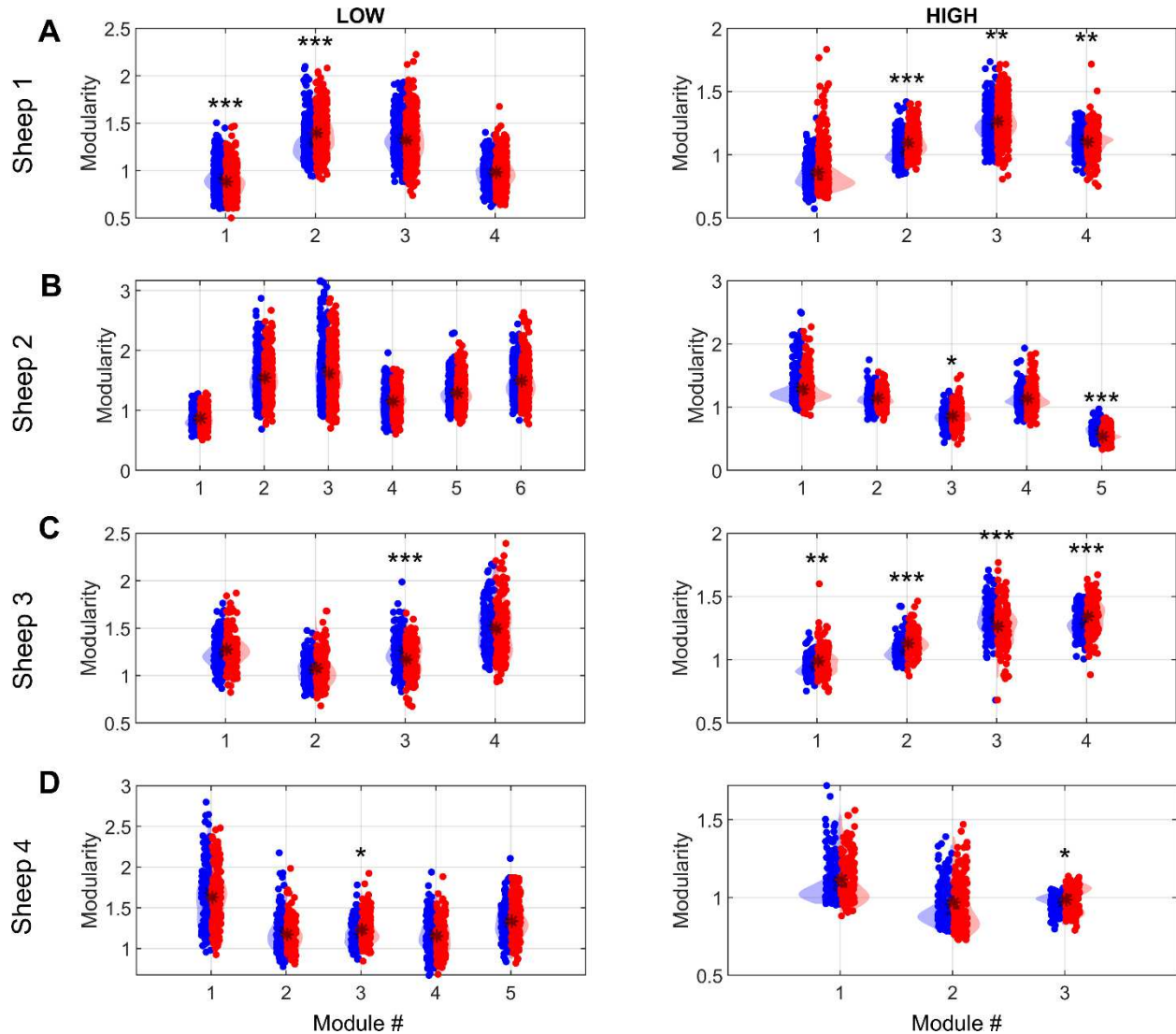


Figure 3: Module-specific changes in cortical modularity across frequency bands. (A) Sheep 1. Low-frequency modules (left) exhibit significant increases in association cortex modules, whereas high-frequency modules (right) show significant increases in Modules 2 and 3 and a decrease in Module 4 following hSCS. (B) Sheep 2. Low-frequency modules (left) show no significant changes, whereas high-frequency modules (right) exhibit significant increases in somatosensory modules and a decrease in an association cortex module. (C) Sheep 3. Low-frequency modules (left) show increased modularity in an association cortex module and decreased modularity in a somatosensory module. High-frequency modules (right) exhibit significant changes across all identified modules, with divergent effects between association and somatosensory cortices. (D) Sheep 4. Low-frequency modules (left) show a single significant change in a mixed association–somatosensory module, whereas high-frequency modules (right) exhibit a significant increase in a somatosensory module. Across animals, module-specific changes were generally more pronounced in the high-frequency modules than in the low-frequency modules, demonstrating frequency-dependent reorganization of cortical modularity following hSCS. Asterisks denote Bonferroni-corrected significance levels ($p < 0.05$, $*p < 0.01$, $**p < 0.001$).

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