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Investigation of 10KHz Spinal Cord Stimulation on Small Fiber Painful Diabetic Neuropathy (PDN)

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Introduction: A large multicenter RCT[1] recently demonstrated that spinal cord stimulation (SCS) at 10 kHz provides effective pain relief for patients with painful diabetic neuropathy (PDN). These outcomes remain durable to 24 months.[2] Patient-reported outcomes suggest profound improvements in pain, function, and quality of life with 10kHz SCS in PDN patients, but more objective quantitative measures of nerve pathology and function can confirm these clinical outcomes and suggest the mechanism of action for the observed clinical improvements.

Methods: This is a single academic center, prospective, open-label, observational study. Inclusion criteria include: ≥18 years of age, type 2 diabetes mellitus, and PDN symptoms >12 months. Exclusion criteria include clinically significant or disabling chronic pain condition other than PDN, expected inability to receive or operate the SCS system, history of coagulopathy, unstable psychiatric disorder, or life expectancy less than 1 year. High-frequency stimulation at 10kHz was utilized. In each patient, skin biopsies to obtain intraepidermal nerve fiber (IENF) density measurements and corneal confocal microscopy measurements were performed pre-SCS implantation and repeated at 3-, 6-, and 12-month time intervals post-implantation. Visual analog scale (VAS), neuropathic pain scale (NPS), Short-Form 36 (SF-36), and Neuropen assessments (10 locations on each foot) were also recorded at each of these timepoints. We report on the pain, skin biopsy, and Neuropen assessments.

Results: Eight patients met the inclusion/exclusion criteria, provided informed consent, and were enrolled. A successful SCS trial was achieved in 7, and 6 completed the study to 12 months. Significant pain relief ($p<0.009$) was achieved at all follow-up visits. Reported VAS at 12 months averaged 27.5±24.3 mm compared to 77.5±16.4 mm at baseline. In addition, the pin prick (Figure 1) and monofilament (Figure 2) neurological assessments showed reduced number of absent responses and increased "normal" responses between baseline and follow-up, aggregating across the patient set, although trends were not statistically significant with the small sample size. Both proximal and distal IENF density trended higher over the course of the study (Figure 3).

Conclusion: We observed increases in lower limb IENF density and improvements in sensory function for PDN patients after receiving 10 kHz SCS. While changes were not statistically significant in the small cohort, these pilot data support that 10 kHz SCS may provide increased small fiber innervation of the lower limb, which leads to sensory improvements in the feet. These results point to the important and unique disease-modifying potential for 10 kHz SCS in PDN patients.

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Identification of Resting-State EEG Markers in Patients With Chronic Pain Before Spinal Cord Stimulation Surgery

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Introduction: Pain is a complex phenomenon resulting from dynamic interactions between sensory, cognitive, and emotional processes[1]. Studying electroencephalography (EEG) signatures of chronic pain can give insights into brain mechanisms of chronic pain and help to characterize the interactions between these dimensions and consequently to develop chronic pain biomarkers. Previous research has showed slower brain oscillations during resting[2] and shifts in alpha frequency correlated with pain duration in patients with chronic pain[3]. We aimed to investigate the resting-state EEG patterns as potential neural markers in chronic pain patients before undergoing Spinal Cord Stimulation (SCS) surgery.

Methods: High-resolution EEG data was collected at rest in addition to the recognized outcome measures including numeric rating scale (NRS), McGill Pain Questionnaire (MPQ) with sensory and affective subscales, Beck Depression Inventory (BDI), Oswestry Disability Index (ODI), and Pain Catastrophizing Scale (PCS), including rumination, magnification, and helplessness. Alpha (8-12 Hz) and theta (4-8 Hz) band powers and their ratio were computed based on our previous study[4]. Additionally, peak frequency distribution across the cortical regions and the correlation between these spectral features and outcome measures were examined.

Results: Pre-operative EEG data from 17 subjects (11 women) with 64.29 ± 2.76 years of age (mean ± SEM) were collected 21.63 ± 6.44 days (mean ± SEM) before their scheduled SCS surgery. Alpha band power was found to be more localized to somatosensory and parietal cortices while theta power was uniformly distributed from anterior to posterior midline. Alpha/theta peak power ratio in logarithmic scale was stronger in the parietal cortices. However, the difference across regions was not statistically significant ($F(2,42)= 1.99$, $p= 0.15$). Peak frequency across all regions was localized to frequencies below 9Hz at the group level. Despite the lack of statistical significance, Spearman's correlation analysis indicated negative trends between the peak frequency (4-12Hz) and the NRS-worst pain scores (5-10) in three regions of interest (ROI): prefrontal cortex (PFC; $r=-0.249$, $p=0.369$), primary (S1; $r=-0.104$, $p=0.712$) and secondary (S2; $r=-0.229$, $p=0.411$) somatosensory cortices.

Conclusion: Our results suggest that stronger theta rhythms in frontal brain areas might be correlated with the pathophysiology of chronic pain. Particularly, trends between the subjective measures and objective markers might indicate that patients with stronger pain had dominantly slower rhythms. Considering that chronic pain biomarkers have not been fully developed yet, these findings might be promising EEG-based neural markers contributing to establishing optimal pain therapies.

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