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Chronic Pain Patients During COVID-19: Machine Learning Reveals Attributes Leading to Pandemic Susceptibility and Resilience

Richard Rauck, MD, Sara Berger, PhD, Guillermo Cecchi, PhD, Carla Agurto, PhD, Elif Eyigoz, PhD, Kristen Lechleiter, MS, Dat Huynh, PhD, Brad Hershey, BS, Eric Loudermilk, MD, Julio Paez, MD, Louis Bojrab, MD, John Noles, MD, Todd Turley, MD, Mohab Ibrahim, MD, Amol Patwardhan, MD, James Scowcroft, MD, Rene Przkora, MD, Nathan Miller, MD, Gassan Chaiban, MD, Matt McDonald, MS, Jeffrey Rogers, PhD

Introduction: The novel coronavirus has disrupted chronic pain patients’ care, on-going clinical studies, interrupted daily routines and pain management plans, as well as halted social/extracurricular activities. These disturbances may contribute to increased pain intensity, worsening disability, and deteriorating mood in a population with mental and physical health comorbidities. COVID-19 presented a unique opportunity to observe patients’ pain experience, including quality-of-life (QoL) and daily activities, as well as identify and characterize individuals who are potentially susceptible to changes during a substantial stressor.

Methods: As part of on-going multi-site Boston Scientific studies prospectively observing up to 1700 chronic leg and back pain patients’ responses to spinal cord stimulation (SCS), we used smartphones to collect daily self-reported pain intensity, mood, sleep, medications, and activities. We also obtained in-clinic questionnaires and objective measures from smartwatches, sleep sensors, weekly voice recordings, and SCS usage. To evaluate changes during COVID-19, we defined two 6-week periods: “COVID” (03/6/2020—04/17/2020), “Pre-COVID” (12/20/2019—01/30/2020). Since patients may be differentially impacted, we performed multivariate analyses integrating changes in self-reported variables between periods, which were normalized and K-means clustered to identify sub-cohorts. We also administered questions to assess patients’ emotional state during the pandemic, analyzed with natural language processing (NLP).

Results: In our results (Figures 1-4), we found no differences in self-reports between pre-COVID and COVID for the entire cohort (n=70/159). However, clustering identified 3 sub-cohorts: individuals whose pain worsened (pain-susceptible), whose activities decreased (ADL-susceptible), and whose mood, sleep, medication, and activities remained the same or improved (QoL-resilient) during COVID. Partial correlations between changes in self-reports also showed differences as a function of period and sub-cohort. Sensor data indicated that NLP-identified fear related speech content during COVID was lower for the QoL-resilient group, who also had greater watch step counts during pre-COVID, supporting the idea that they had the best overall wellbeing or initial behaviors of the 3 groups. There were no differences in clinical assessments or SCS usage between sub-cohorts or periods.

Conclusion: Our results indicate the existence of 3 patient sub-cohorts that diverge in their behaviors during COVID-19. We find each sub-cohort has a characteristic signature that allows us to predict the response an individual patient had to the pandemic. These findings demonstrate the importance of multi-dimensional digital monitoring with important implications for telemedicine, clinical trials and neuromodulation system management.

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Figure 3. Partial correlations for self-reported variables. Spider plots show conditional relationships (partial correlations) between self-report ratings across the 3 sub-cohorts (X-axis) for both pre-COVID and COVID periods (Y-axis). Differences between plots can be visually appreciated. Nodes in plots indicate each of the 12 self-reported ratings (or combination of ratings). Lines indicate partial correlations between self-report variables (correlations after accounting for all other relationships between variables); line color is the direction of correlation (positive = red; negative = blue) and line thickness/saturation indicates strength of correlation (larger r-values = thicker, darker lines; smaller r-values = thinner, lighter lines). Only the strongest (significant or trending) correlations are shown, if no line is present, variables were conditionally independent, or correlations were not statistically strong. Abbreviations: Sleep-Q (sleep quality); Sleep-Hrs (sleep hours); Rx (non-opioid prescription medications for pain indication); OTC (over-the-counter medications); Sleep-Ms (sleep medications); B-SelfCare (basic activities and self-care activities, including eating, cooking); Exercise (includes exercise, housework, and yard-work); Commute (includes all forms of traveling).

Figure 4. Boxplots of features from subset of objective measurements. We collected objective (non-self-reported) features from patients, including but not limited to voice recordings and smart watch features. (a) NLP features captured from voice recordings of a questionnaire administered during a one-week timeframe in the COVID period show differences between the 3 sub-cohorts in emotional responses to the pandemic. (b) Smart watch step-counts from n=50 out of 70 patients compared between groups for both pre-COVID and COVID periods; step counts were totaled per day and averaged across each period. * at the top of the boxplot indicates if the values for the features are significantly different among the 3 clusters (Kruskal-Wallis test, p-value < 0.05). ** indicates the values for the features are significantly different among the 3 clusters (Kruskal-Wallis, p-value < 0.01).
Selective Activation of Dorsal Horn Neurons by Various Spinal Cord Stimulation Strategies

Kerry Bradley, MS, Kwan yeop Lee, PhD, Dongchul Lee, PhD, Zachary Kagan, PhD, DONG WANG, PhD

Introduction: In spinal cord stimulation (SCS) for chronic pain, various stimulation strategies (10 kHz, asymmetric biphasically-recharged burst [AB], and passively-recharged burst [PB]) have been clinically applied, though the mechanisms for these various strategies are not yet clear. Here, we investigated the responses of superficial dorsal horn neurons (SDHN) classified as adapting excitatory (AE) & non-adapting inhibitory (NAI) neurons to different SCS strategies.

Methods: Adult male Sprague Dawley normal rats under urethane anesthesia were used. In all experiments, after multi-level laminectomy, SCS was applied via a micro-sized, in-line quadripolar electrode array positioned epidurally over the L5-L6 dorsal spinal segments (innervating the left hind paw). A 4-pronged, 16-contact extracellular recording electrode (NeuroNexus16ch, Ann Arbor, MI) was plunged into the SDH (depth from cord surface: 300±50um) within 1mm of the active contacts on the quadripolar SCS array. First, we defined the receptive field center of SDHN by their most active response to brush and von Frey (VF) stimuli onto the ipsilateral hind paw. Then, we identified the neurons as AE or NAI cells by their firing response to 10g VF, depth of location, etc. Twenty trials of each SCS strategy (10kHz, AB, PB) at 30% of motor threshold were applied for 20sec with an intervening 2sec no-stim interval. At least 5min of quiescence was allowed between application of different strategies. Mean firing rate of neurons and Selective Activity Ratio (SAratio = firing rateNAI / firing rateAE) were analyzed as the response to SCS.

Results: In 6 rats, we found 21 NAI and 22 AE neurons. 10 kHz SCS produced 3-4x greater firing rate responses among NAI neurons compared to PB or AB (P<0.05), whereas it produced minimal (2-3.5x less) firing rate responses of AE neurons (P<0.01). By SAratio, 10 kHz SCS was 6-17x more selectively active than to NAI neuron firing relative to AE neuron firing than both burst strategies (P<0.05).

Conclusion: We observed, at stimulation intensities that would ostensibly not activate dorsal columns (i.e. "paresthesia-free"), that 10kHz selectively activates NAI neurons at higher rates and with more selectivity than PB and AB burst SCS. This suggests that 10 kHz SCS and burst strategies likely operate via different mechanisms.

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