Supplementary Material: Analysis Methods

Aggregation of data across multiple SCS studies is helpful for reducing influence of potential confounding factors unique to any single site or setting. To identify relationships between optimized therapy programming and patient outcomes, physiologic data was analyzed in the week preceding the follow-up visit at which patients reported maximum percent pain relief from baseline[1–4]. The rationale for using this maximal analgesic effect (MAE) visit is to capture one datapoint per patient that reflects their most optimized program and therapy regimen. A program encompasses a set of device parameters that determine the delivery of stimulation through a subset of electrodes. MAE days from permanent implant ranged from 7-1674 days with a median of 102 days and interquartile range of 42 and 307 days [7,8,11].

Activation plots (APs) characterize the relationship between stimulation current at a fixed pulse width and neural activation measures. APs are recorded during regularly scheduled visits and follow-up visits. During these visits, the SCS programmer will set up stimulation using a given program, and then increase the current of the program with the patient in a single posture (most commonly a sitting posture). A correlation filter is used to transform the measured ECAP into an estimate of its amplitude with respect to the PCLCS in operation. Aβ fibers are not activated below a threshold stimulation level, so no ECAPs can be measured below this level. Above the threshold level, the ECAP amplitude increases with increasing stimulation current[5–8]. The threshold level of the activation plot is defined here as the point at which the AP begins to inflect up.

To estimate the threshold of activation, each AP is fit to the model described by Equations (1) and (2) using Levenberg-Marquardt non-linear regression.

$$\hat{V}(I) = b_{artefact} + m_{artefact} \cdot I + P \cdot I_0 \left(g_{r=1,\tau}\left(\frac{I}{I_0}\right) - g_{r_{saturation},\tau}\left(\frac{I}{I_0}\right) \right) \quad (1)$$

$$g_{r,\tau}(x) = \tau \log\left(e^{-\frac{x-r}{\tau}} + 1\right) + (x - r) \quad (2)$$

The model parameters are described in Table 1.

$b_{artefact}$	An intercept term associated with the steady state artefact contribution to the feedback variable.
$m_{artefact}$	The slope of the current dependent artefact contribution to the feedback variable.
P	The AP sensitivity parameter. Equivalent to slope of the linear portion of the AP for $I > 1.2 \times I_0$.
I_0	A current normalisation parameter.
$r_{saturation}$	A parameter representing the ratio of the activation threshold and the point at which the AP saturates.
τ	A curvature parameter. Determines the 'bend radius' of the AP fit function.

Table 1: Fit parameters associated with Equations (1) and (2).

The fit function and non-linear regression where validated against a subset of 2048 APs, and goodness of fit evaluated using the Akaike Information Criterion (AIC)[5,9] for both Equation (1) and the piecewise linear model previously published . AIC was found to be smaller for 70% of APs and was within 5 points of the piecewise linear AIC for the majority of the remaining 30% of cases.

Threshold is estimated as the point at which Equation (1) inflects above the smaller of ½ a standard deviation of the noise contribution to the ECAP amplitude measurements or 5μV. The standard deviation of the ECAP noise is calculated by subtracting Equation (1) from the observed ECAPs for $I < I_0$ and measuring the standard deviation of the difference. The upper bound of 5μV corresponds to the upper limit of the noise contribution of the recording electronics of the Evoke system and acts as a fallback in cases where the measured standard deviation overestimates the true ECAP noise contribution due to low sample counts.

This method of estimated threshold is advantageous as it only relies on Equation (1) fitting the data well and is not influenced by how well constrained the model parameters are, which can be negatively impacted in APs with poor signal to noise ratio. This threshold definition further has the advantage that it is insensitive to the extent of the activation plot above threshold and is therefore unbiased by differences in the extent of each patient's maximum level.

The maximum stimulation amplitude is set based on the patient's self-reported maximum, and it is programmed as a current cap that may not be exceeded. Typically the cap is set above the stated maximum to allow for adequate therapy in positions that require more current. Because this cap well exceeds the typical operating levels, it is not related to the median FBV levels used as a basis for measurement here.

Dose accuracy

$$= \sqrt{\sum_{i=1}^{n} \frac{\left(ECAP_{measured} - ECAP_{target}\right)^2}{n} - \sum_{j=1}^{n_2} \frac{\left(ECAP_{baseline\_measured} - ECAP_{baseline\_mean}\right)^2}{n_2 - 1}}$$

The accuracy metric is calculated from the target and recorded ECAP and reported in μV rather than as a ratio because the loop operates in the μV domain to maintain the target. While a ratio could be calculated for accuracy, the absolute μV metric is used here to better approximate absolute error as it pertains to the device operation. We included only datapoints for which the target was over threshold (dose ratio >=1) to ensure the accuracy has a meaningful value: it is not simply reflecting the measurement noise but rather changes in the measured ECAP with activities of daily living.

Data for each metric was tested for trend as shown in Figure 2. To focus on the most representative data range for each metric, the 5th to 95th percentile of available metric values (not all patients had values for all metrics) was rounded to the nearest number corresponding to the order of the data (tens for utilization, ones for variability, and tenths for dose ratio). In all cases, this remained inclusive of >90% of patients with accompanying values and enabled linear spacing on a relevant range of values. Each metric was grouped linearly in the determined range of values and a Jonckheere-Terpstra one-tailed test for trend performed on the grouped outcome metric difference from the overall median outcome[10]. The population median MAE against which differences in each subgroup are judged was 78% pain reduction for device utilization, 79% for therapy utilization, 80% for dose ratio, and 82% for out-of-clinic dose accuracy. The exception to strictly linear metric grouping was the subthreshold dose ratio, which was grouped all together as 0-1. All subthreshold dose ratios are expected to elicit only sporadic activation of the dorsal columns, and the exact ratio of the measured activation is not precise at values below 1. This grouping of dose ratios less than 1 guards against spurious subthreshold ratio values that

occur as a result of mapping a recorded median activation level to a relatively flat subthreshold region of the AP.

To confirm robustness of the resulting significance from the Jonckheere-Terpstra test with unequal populations in each bin, the data were randomly shuffled 1000x and reassigned with population numbers in each bin matching the original unequal populations. The p-values found in the non-randomized sample remain significant in comparison with the 5th percentile p-values found in the randomized sample in all cases.

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