**Recruitment curve analysis**

**TMSstroke\_RC\_v3.Rmd**

This was the original script that used a variation of the Boltzmann equation for fitting the RC data to a sigmoid curve. However, ran into singular gradient matrix error at initial parameter estimate.

**Rationale for this script:**

The Boltzmann equation is commonly employed in literature to model recruitment curves. Two variations of the logistic equation are frequently used for this purpose:

**Function 1:**

y = min + [(max - min)/(1 + exp((S50 - x)/slope))]

**Function 2:**

y = min + [(max - min)/(1 + exp(slope\*(S50 - x))]

In Function 2, the slope parameter is the inverse of the Boltzmann equation's slope parameter. An increase in the slope parameter signifies a larger increment in Motor Evoked Potential (MEP) size per unit of stimulus intensity, unlike the Boltzmann slope parameter - this is what is used in the script.

The Levenberg-Marquardt algorithm is widely employed for model convergence in fitting these curves to data. Notably, the nlsLM function from the minpack.lm R package is preferred over the standard nls function, as it utilizes the Levenberg-Marquardt algorithm.

Key output parameters of interest include:

1. **Plateau:** Maximum amplitude (mV)

2. **S50**: Stimulus intensity x (%MSO) at which MEP size is 50% of the maximal MEP

3. **Slope**: MEP amplitude increase with each percentage point of stimulator intensity increase (mV/%MSO)

The slope parameter is considered a valuable measure of cortico-spinal excitability, providing a reliable estimate of the increase in EMG response for a given stimulus intensity. This is in contrast to the maximum of the input–output relationship (MEPmax), which has lower reliability due to factors such as phase cancellation at recording electrodes.

Several papers (cited) detail the application of these models and algorithms in estimating recruitment curve parameters. Log transformation of MEP amplitudes is sometimes employed for analysis.

Useful papers:

* http://dx.doi.org/10.1016/S0165-0270(01)00468-X
* http://dx.doi.org/10.3389/fncel.2015.00335
* http://dx.doi.org/10.3389/fnins.2016.00079
* http://dx.doi.org/10.1109/TNSRE.2019.2914475
* http://dx.doi.org/10.1113/jphysiol.2002.029454
* DOI:10.1177/1545968307300437
* http://dx.doi.org/10.1016/j.clinph.2015.05.017

**TMSstroke\_RC\_v4.Rmd**

This is another version of the script that was developed with Dr. Malcolm Binns’ help. The following changes were made:

We got Participant #18989 to fit, both pre and post, by doing the following:

(a) constrained the maximum level of the function based on the maximum amplitude achieved at either pre- or post- sessions

(b) changed the nls optimization method to "port"

(c) changed the function from logistic to the hyperbolic tangent

See bottom section of the script for single-subject fitting of the model. The first section of the script is an attempt to try to automate the process of fitting this model to all of the subjects, however, we ran into the same singular gradient matrix error at initial parameter estimate error as above.

We encountered challenges with the model convergence for both models in v3 and v4 scripts. It became apparent that starting values need to be very close to the actual values for the models to converge successfully. In an attempt to address this issue, we applied a trace on a subject to estimate starting values (subject 18989 at the bottom of the script). However, applying these estimated starting values uniformly across all subjects proved ineffective. Since trying to apply these same starting values to all subjects didn't work, this makes it difficult to hard code them into the function.

Malcolm said R might be fiddly here and that there might be stronger non-linear fitting software available, but he's not familiar with them. He said the worst case scenario is to plot the observations and fitted line for each subject separately, and use those to help determine starting values. This does mean that in its current state, it is unfortunately not an automated process and will need to be separately done for each subject to get their values.

**Resting-Motor Threshold (RMT) analysis:**

**TMSstroke\_RMT.Rmd**

This script analyzes and visualizes resting motor threshold (RMT) data, comparing pre- and post-treatment measurements for affected and unaffected hemispheres using two different coil sizes (70mm and 50mm). Although it looks at both coils and both hemispheres, the only statistically significant results will come from the 70mm coil (typically reported in the literature), and from the unaffected hemisphere (since only 3 subjects had an MEP on the affected hemisphere).

* Conducts paired t-tests on the RMT values for affected and unaffected hemispheres separately for each coil size and time point.
* Calculates effect sizes (Cohen's d) for each t-test.
* Creates boxplots to visualize the distribution of RMT values before and after treatment, separately for each coil size and hemisphere.
* Adds p-values and significance levels to the boxplots.

**Short-interval intracortical inhibition (SICI) analysis:**

**TMSstroke\_SICI.Rmd**

Amplitude Analysis:

SICI amplitude is reported as follows: the mean MEP amplitude was calculated for each state, and this MEP was then expressed as a ratio or percentage of that resulting from a single pulse (conditioned (CS+TS)/unconditioned (TS)).

* For affected and unaffected hemispheres, paired t-tests are conducted to compare pre and post-treatment MEP amplitudes.
* Cohen's d effect sizes are computed.

Latency Analysis:

For changes in latency, look at TS alone. I don't think a ratio of latencies is commonly used for SICI.

* Similar to amplitude analysis, paired t-tests and effect size calculations are performed for latency.

**Rationale:**

SICI amplitude = (state 2/state 1)×100

Expect a reduction in Short Interval Intracortical Inhibition (SICI) following training. Higher SICI values imply less inhibition, while lower SICI values indicate more inhibition.

Preliminary analysis of RMT (Resting Motor Threshold):

* Observed a decrease in RMT in the unaffected hemisphere, indicating increased cortical excitability.
* Consequently, anticipate finding lower SICI, suggesting more local inhibition in the unaffected hemisphere.
* Propose that larger increases in contralesional (unaffected hemisphere) excitability will be associated with enhanced evidence of Transcallosal Inhibition (TCI), indicative of greater connectivity between hemispheres.

References:

* DOI: 10.1177/1545968314533613: Peak-to-peak MEP amplitude (mV) was determined and SICI calculated as a percentage of the non-conditioned response, with % inhibition derived by subtracting from 100. Change in percentage inhibition was calculated for each hemisphere.
* DOI: 10.1177/1545968310376757: SICI and ICF were determined by calculating the mean MEP amplitude for each state, expressed as a percentage of the single-pulse response (conditioned/unconditioned).
* http://biomedcentral.com/2052-1847/6/23: For SICI and ICF, the average amplitude elicited by the conditioned stimulus was expressed as a percentage of the average unconditioned MEP amplitude at 120%.
* DOI: 10.1007/s00221-014-3879-z: Studies in humans indicate enhanced neuroplasticity when SICI is reduced. An exercise-induced reduction in SICI may facilitate increased neuroplasticity, particularly in the acute stage following aerobic exercise.

**Repeated measures correlation (rmcorr) analysis for RMT and SICI with behavioural ARAT data:**

**TMSstroke\_rmcorr.Rmd**

The script employs the **rmcorr** package for repeated measures correlation analysis and **ggplot2** for data visualization. The **rmcorr** package and analysis is based on the following paper: <https://www.frontiersin.org/articles/10.3389/fpsyg.2017.00456/full>

The script first performs repeated measures correlation analysis and generates a plot for RMT vs ARAT (behavioural measure of functional hand ability). It then repeats it for SICI amplitude vs ARAT, as well as for SICI latency vs ARAT. Determination of SICI amplitude and latency is discussed in the section above.

**Long-interval intracortical inhibition (LICI) analysis:**

This will likely be a very similar analysis to **TMSstroke\_SICI.Rmd**.

Peak-to-peak amplitudes of the test MEP were measured from individual trials and the mean test MEP amplitude was calculated across all trials. For MEPs, LICI strength was calculated by comparing conditioned test responses (paired-pulse) to unconditioned test responses (single-pulse) using:

LICI = (MEPsingle - MEPpaired)/MEPsingle × 100