PROTOCOL TITLE: Electroconvulsive therapy amplitude titration for improved clinical outcomes in late-life depression

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1. Data Analysis

Preliminary Data: Amplitude titration has been completed with non-human primates but has yet to be completed with human subjects and modern ECT parameters. *I/E_{brain} bridges the gap from amplitude titration in non-human primates to changes in hippocampal neuroplasticity in human subjects.* I/E_{brain} is the ratio of electrode current strength (I) to the E-field strength in the brain (E_{brain}) [21]. E_{brain} will be computed as the 90th percentile of E-field magnitudes from all voxels in the brain, serving as an estimate of the peak induced field strength while avoiding the influence of tissue boundary effects that could bias the absolute maximum E-field values. For example, one subject with 800 mA extracranial amplitude produces 0.8 V/cm 90th percentile E-field strength. The ratio would be 1000 mA/V/cm, which means 1000 mA produces 1 V/cm. A second subject with the same 800 mA extracranial amplitude produces 1.2 V/cm 90th percentile E-field. The ratio would be 667 mA/V/cm, which means 667 mA produces 1 V/cm. E_{brain} is a whole brain E-field metric as the location of seizure duration is unknown.

The relationship from amplitude titration to hippocampal neuroplasticity is illustrated here (**Figure 4**). First, we demonstrate that amplitude-titrated seizure threshold increases with I/E_{brain} in non-human primates (**4A**). Second, we demonstrate that increased I/E_{brain} is related to decreased hippocampal E-field (current dependent metric, input current set here at 1 mA) (**4B1**). For fixed amplitude ECT, I/E_{brain} is inversely related to hippocampal volume change. E_{hippo} is the 95th percentile E-field in the hippocampus and will be an exploratory measure of this investigation. However, the focus on amplitude titrated seizure threshold requires E_{brain}, a whole brain E-field metric, as the regions involved in seizure induction are unknown. Third, we demonstrate that increased hippocampal E-field is related to increased hippocampal neuroplasticity across all amplitudes (600, 700, and 800 mA) and electrode placements (RUL and BT) (**4B2**). This relationship is a replication of the GEMRIC data (Figure 2) with our U01 data. Fourth, we performed an analysis of a subset of our data comparing I/E_{brain} with hippocampal volumetric change with 800 mA subjects (**4B3**).

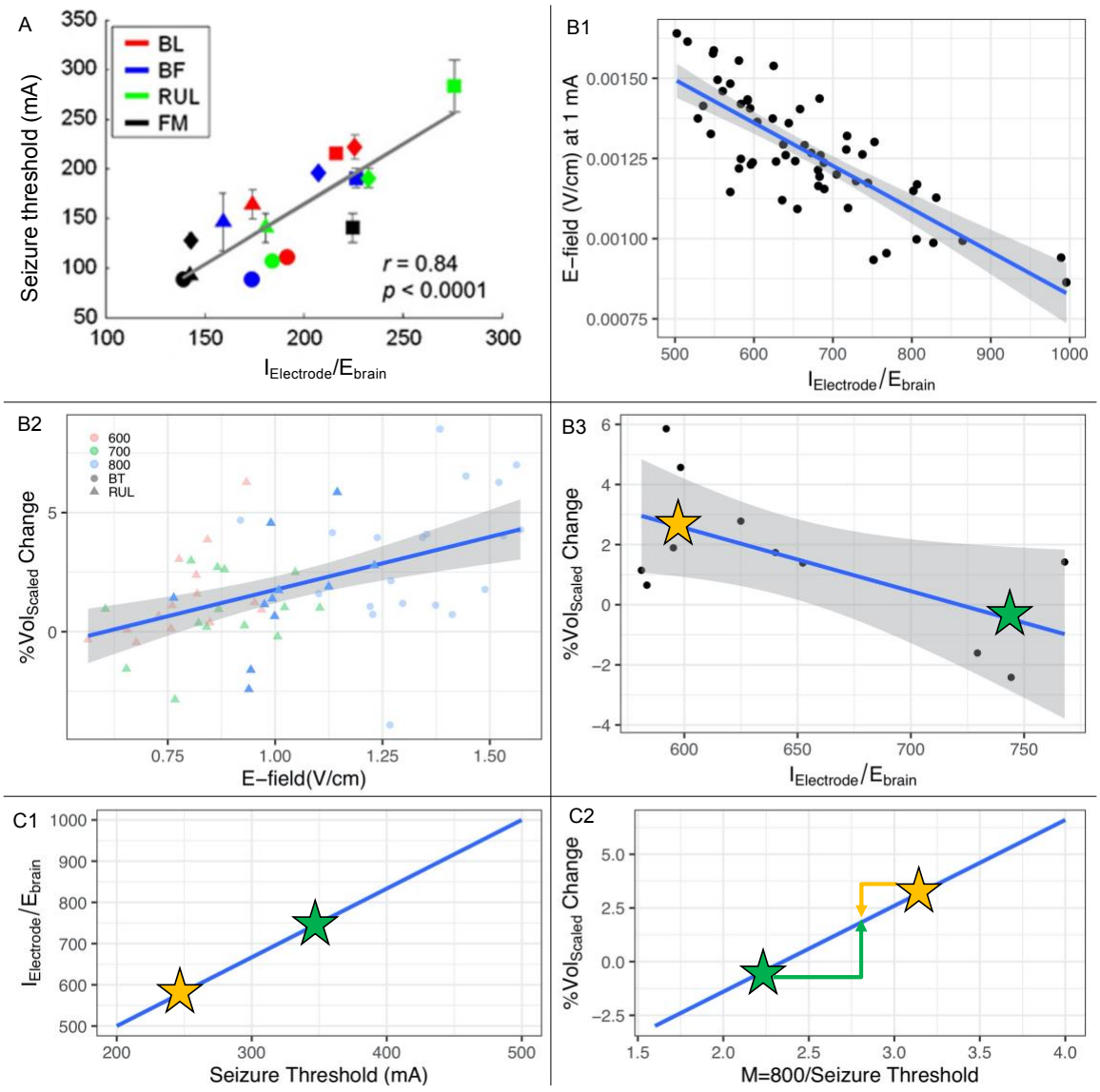

Figure 4: The multi-step relationship from amplitude titration to hippocampal neuroplasticity.
A) Non-human primate data. $I_{electrode}/E_{brain}$ (see description in Preliminary Data). Increased I/E_{brain} is related to increased amplitude required for seizure titration ($r = 0.84$, $p < 0.0001$).
B1) U01 data, all subjects. $I_{electrode}/E_{brain}$ is inversely related to hippocampal E-field magnitude with an amplitude intensity of 1 mA, which is baseline for E-field modeling ($r = -0.79$, Cohen's $f^2 = 1.66$).
B2) U01 data, all subjects. Electrode placement (RUL and BT) and amplitude (600, 700, 800 mA) are based on the subject's last treatment. Right hippocampal E-field magnitude is directly related to right hippocampal neuroplasticity for all amplitude strengths (600, 700, and 800 mA) and electrode placements (right unilateral and bitemporal) ($r = 0.49$, Cohen's $f^2 = 0.33$).
B3) U01 data, subjects from the 800 mA arm. $I_{electrode}/E_{brain}$ is inversely related to right hippocampal neuroplasticity for 800 mA subjects ($r = -0.62$, Cohen's $f^2 = 0.62$).
C1) Hypothesized relationship. Increased $I_{electrode}/E_{brain}$ is related to increased amplitude required for seizure titration (verification of non-human primate data depicted in 4A).
C2) Hypothesized relationship (Go-No-go). The ratio of fixed amplitude ECT (800 mA) relative to amplitude seizure titration will be associated with right hippocampal neuroplasticity.

Summary,

interpretation, and alternatives: To illustrate the application of these principles, we use our preliminary data (**4B3**) and hypothesized relationships (**4C1** and **4C2**). We also use the example of 2% hippocampal growth as optimal for antidepressant response (optimal hippocampal growth will be determined with a receiver operating curve

(ROC) curve predicting Inventory of Depressive Symptomatology (IDS-C_{30}) total score decrease during the R61). With traditional 800 mA amplitude, the 2% volume increase is related to an I/E_{brain} of ~ 625 mA/V/cm (**4B3**) and fixed/amplitude ratio of ~ 2.7 (**4C2**). Subject #1 (orange star) has a low (250 mA) seizure threshold (ST) (**4C1**), I/E_{brain} of ~ 600 mA/V/cm (**4C2**) and a fixed/amplitude ratio of 800/250 = 3.2 (**4C2**). Subject #1 will need an input current of $2.7 \times ST = 2.7 \times 250\,mA = 675\,mA$ for 2% hippocampal volume increase. In contrast, Subject #2 (green star) has a high (350 mA) seizure threshold, I/E_{brain} of ~ 750 mA/V/cm and a fixed/amplitude ratio of 800/350 = 2.3. In order to achieve the 2% volumetric increase, Subject #2 will require an increased X/amplitude ratio from 2.3 to 2.7. Subject #2 will need an input current of $2.7 \times ST = 2.7 \times 350\,mA = 950\,mA$ for 2% hippocampal volume increase. We stress that the fixed/amplitude ratio ~ 2.7 for 2% hippocampal volume increase is conceptual and will be determined during the R61.

H1: Amplitude seizure titration will have a positive correlation with I/E_{brain} (**Figure 4C1**). This is a replication of the data from the non-human primate data. The relationship between I/E_{brain} and amplitude titration is the foundation for the rationale of this proposal.

Statistical approach for H1: Let $(x, y)_i$ be the observed vector of response for I/E_{brain} and seizure threshold for each patient, I = 1, …, n. The Pearson correlation will be calculated and the standard one-sided t-test with 2 degrees-of-freedom will be conducted for testing whether the correlation is positive, H_0: $\rho > 0$.

Power calculation for H1: The observed correlation in Figure 4A is $r = 0.84$ for non-human primates and we expect that the more conservative Cohen's "large" effect size $r = 0.5$ is a realistic lower bound for our population, thus a sample size of n = 29 provides 80% power at a 0.05 / 2 = 0.025 significance level.

Go/No-Go criterion (H2): The ratio of amplitude titration to fixed amplitude ECT will demonstrate a linear relationship with treatment-responsive changes in hippocampal neuroplasticity. This relationship will determine the "neuroplasticity multiplier" to bridge from amplitude titration to hippocampal neuroplasticity.

Statistical approach for H2: We will perform a multiple regression accounting for covariates age and sex, $\%Vol_{Scaled}$ Change = $\beta_0 + \beta_1$ M + β_2 age + β_3 sex, where the effect size is $f2 = R^2 / (1 - R^2)$, with R^2 the coefficient of determination with the interpretation of "the proportion of variance explained" in the response by the model over the grand mean. We will test whether the regression model explains a significant proportion of variance in the response, expecting that the key relationship is between $\%Vol_{Scaled}$ change and multiplier M.

Power calculation for H2: The relationship we are expecting in Figure 4C2 is derived from Figures 4B3 and 4C1. Starting with Figure 4B3, the relationship of I/Ebrain on $\%Vol_{Scaled}$ change has a correlation of $r = -0.62$ with an effect size f2 = 0.624, well above the Cohen's "large" effect size of f2 = 0.35. Figure 4C1 is Figure A with the axes reversed, thus the correlation is $r = 0.84$. We will assume that the relationship between $\%Vol_{Scaled}$ Change and multiplier M will remain consistent with Cohen's "large" effect size. Then a sample size of n = 36 provides 80% power at a 0.05 significance level.

The Holm Procedure, a multi-step step-down procedure useful for endpoints with any degree of correlation, will adjust the two hypotheses below for multiple comparison [37]. For our situation, this means H1 is tested at the 0.05 / 2 significance level and H2 is tested at 0.05 / (2−1) = 0.05; however, H2 is tested only if H1 is significant.

The Go/No-Go criterion is set to "Go" if we can reject the null hypothesis that H_0: β_1=0 at a 0.05 significance level in the model specified in Hypothesis H2, that is, that multiplier M remains a significant predictor of $\%Vol_{Scaled}$ Change after adjusting for age and sex.