# Cardiac Vagal Control: A biomarker for subject selection in subcallosal cingulate deep brain stimulation for treatment resistant depression?

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## BACKGROUND

Major Depressive Disorder is associated with aberrant autonomic function, as determined by cardiac vagal control (CVC) and indexed by a reduction in resting state heart rate variability (HRV) (Bassett et al., 2016)[1].

Mayberg et al. 2005[2] targeted the subcallosal cingulate (SCC) with deep brain stimulation (DBS) and observed clinical benefits in patients with treatment-resistant depression, as evidenced by reductions in Hamilton Depression Rating Scale (HDRS-17) scores.

The SCC is part of the central autonomic network, which is involved in vagal function that regulate the cardiac cycle (Lane et al., 2013[3]; Riva-Posse & Mayberg 2014,[4] Patricio et al. 2019[5] ).

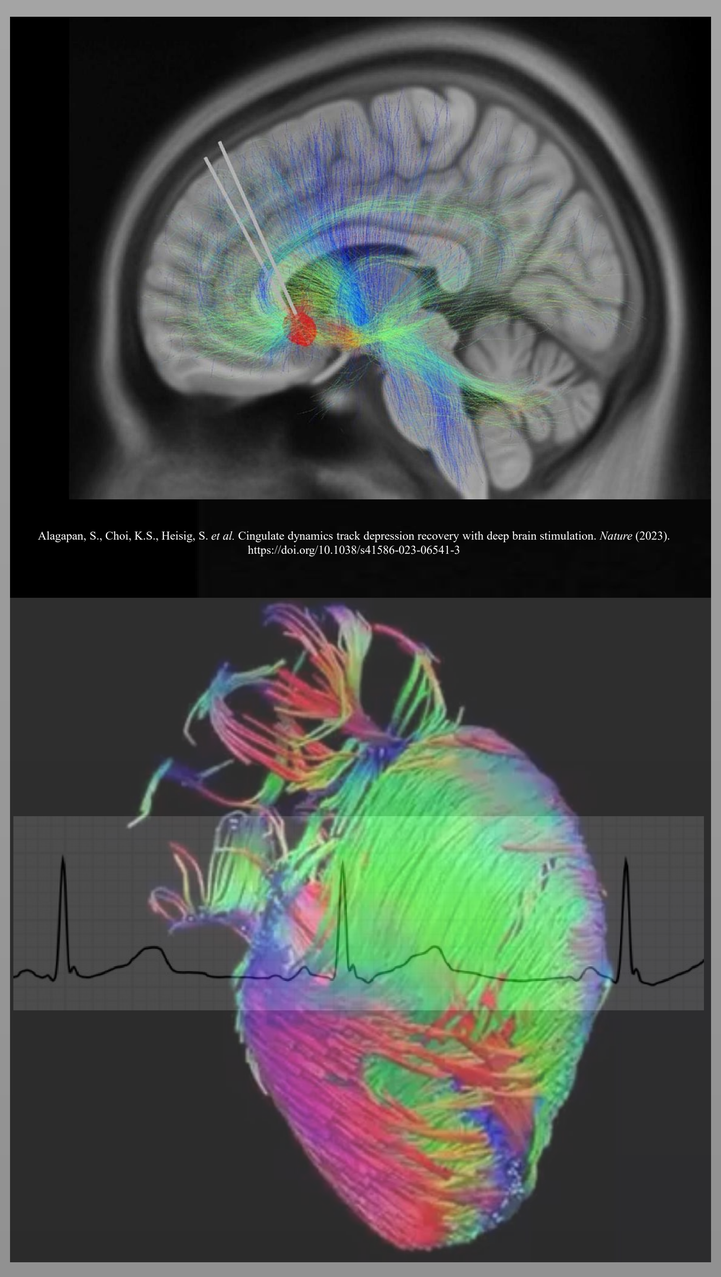
SCC DBS may impact autonomic function.

## OBJECTIVES

a. Does SCC DBS influence cardiac vagal control (CVC) and depressive symptoms (HDRS-17) across treatment and stimulation?
b. Does baseline CVC predict symptom severity and time to sustained treatment response? Does baseline symptom severity predict overall change in CVC?

## HYPOTHESES

1) An increase in HRV and a decrease in clinical symptoms with SCC DBS.
2) Greater baseline HRV will predict a quicker time to sustained response (defined as the number of weeks preceding a 50% symptom reduction or greater on the HDRS -17, maintained for a min of 2 consecutive weeks).
3) Greater baseline HDRS -17 will be associated with more HRV change over time.



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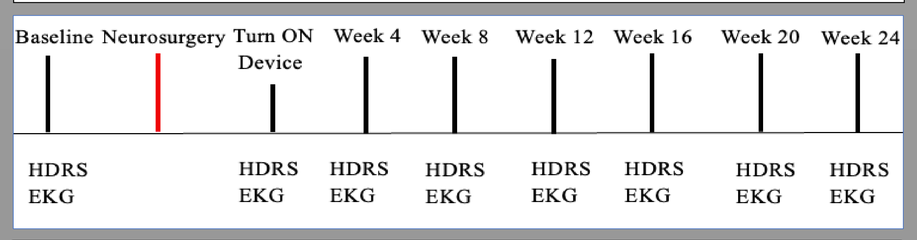
## METHODS

*Subjects:*

Nine subjects with treatment – resistant major depressive disorder received neurosurgical implantation of two leads in the subcallosal cingulate cortex; Clinical Trials ID: NCT01984710). *One subject excluded from analyses due to anticholinergic medication that acts as a confound on vagal activity (n=8).

*Procedure*:

a. Monthly laboratory visits for 6 months (timeline below).
b. Respiration and EKG recorded at a rate of 1000 samples per second during each time point.
c. HDRS - 17 acquired at each timepoint.
d. Conditions (3-5 minutes):
   i. DBS ON (Bilateral, 130 Hz 90us), DBS OFF




*EKG Preprocessing and CVC Extraction:*

- Lowpass filter (50hz) applied to EKG.
- R-spikes identified and interbeat interval (IBI) series extracted in QRSTool[6].
- The root mean square of successive differences (RMSSD) between adjacent r-spikes was calculated to reflect vagal influence on heart rate.
- The natural log of the variance in the IBI time series within the high frequency range (.12hz - .40hz) was calculated to reflect Respiratory Sinus Arrythmia (RSA). RSA and RMSSD are highly correlated (r =.84, p <.001).

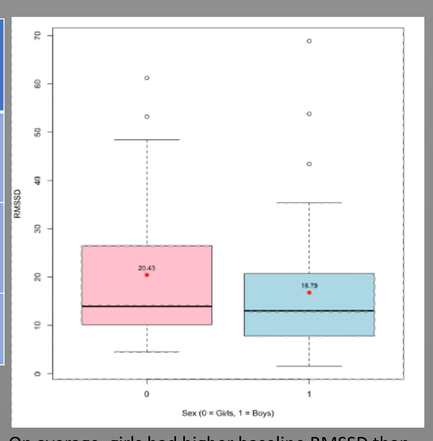
## RESULTS

**Table A: Group Baseline Averages of CVC (RMSSD) and Heart Rate**

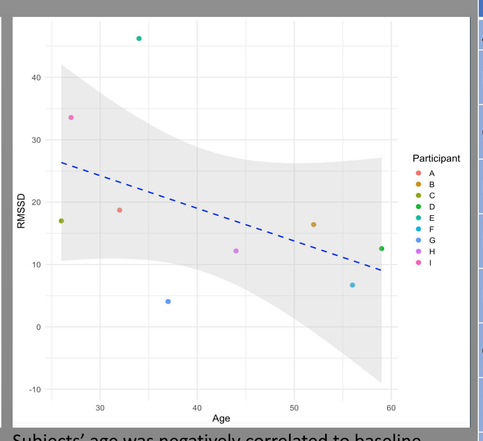
| Baseline Average | n = 8 Mean (SD) |
|---|---|
| RMSSD (ms) | 20.76(21.72) |
| RSA (HF Power) | 4.38 (1.55) |
| Heart Rate (BPM) | 79.38(12.51) |

A study by Thayer et al. (2024)[7] in 9,972 adults found that an RMSSD of 25 ± 2 ms or lower was associated with a 39% increased risk for depression. Our average RMSSD (20.76 ms) is lower than this threshold, suggesting a potential marker for treatment resistant depression in our sample.

**Figure 1. Sex and Age-Related Changes in Baseline RMSSD**




On average, girls had higher baseline RMSSD than boys, although this difference was not statistically significant (t(8) = 1.53, p = 0.13)

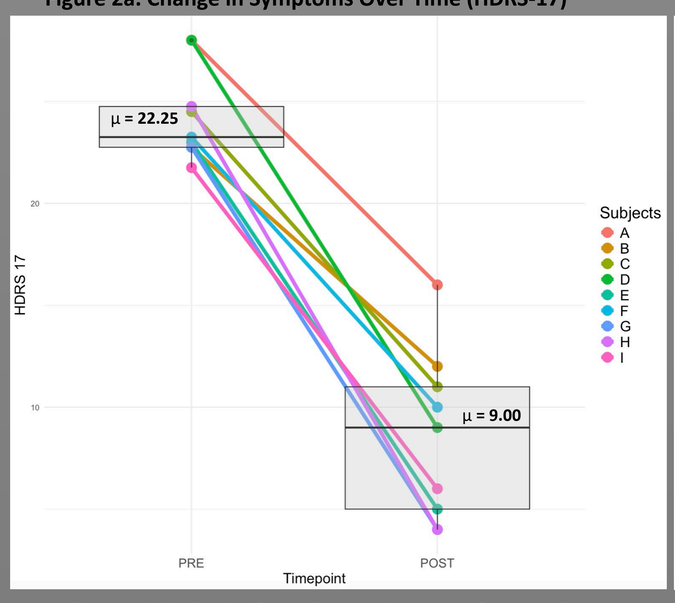



Subjects' age was negatively correlated to baseline RMSSD, Pearson's r = -.48, t(8) = -1.486, p = .18, suggesting younger subjects have higher RMSSD values.

**Table B: Demographics**

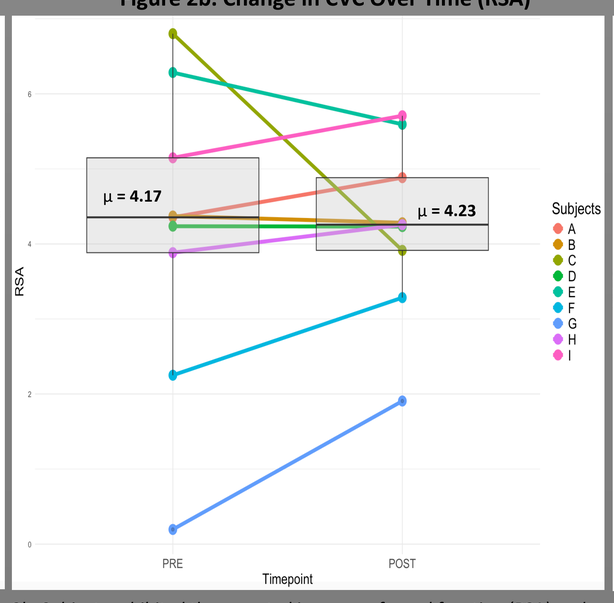
| Subject | Sex | Race | Age at study entry (yrs) | HDRS -17 | RMSSD | RSA | HR |
|---|---|---|---|---|---|---|---|
| A | F | White | 32 | 21 | 18.72 | 4.60 | 86.19 |
| B | M | White | 52 | 13 | 16.40 | 4.53 | 74.41 |
| C | F | White | 26 | 12 | 16.99 | 4.98 | 86.20 |
| D | M | White | 59 | 17 | 12.55 | 4.09 | 80.40 |
| E | F | White | 34 | 10 | 46.23 | 6.30 | 64.77 |
| F | F | White | 56 | 14 | 6.69 | 2.14 | 62.33 |
| G | M | White | 37 | 13 | 4.06 | 1.67 | 107.64 |
| H | M | White | 44 | 11 | 12.17 | 3.37 | 86.75 |
| I | F | White | 27 | 11 | 33.56 | 6.10 | 80.80 |

**Figure 2a. Change in Symptoms Over Time (HDRS-17)**



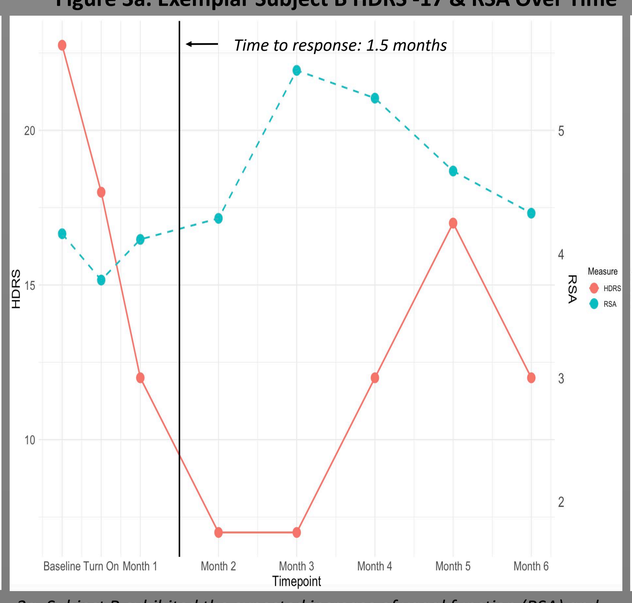

*2a.* Subjects exhibited a significant decrease in HDRS-17 from Baseline to Week 24 of SCC DBS *t(8) = 8.9417, **p<.001.*

**Figure 2b. Change in CVC Over Time (RSA)**



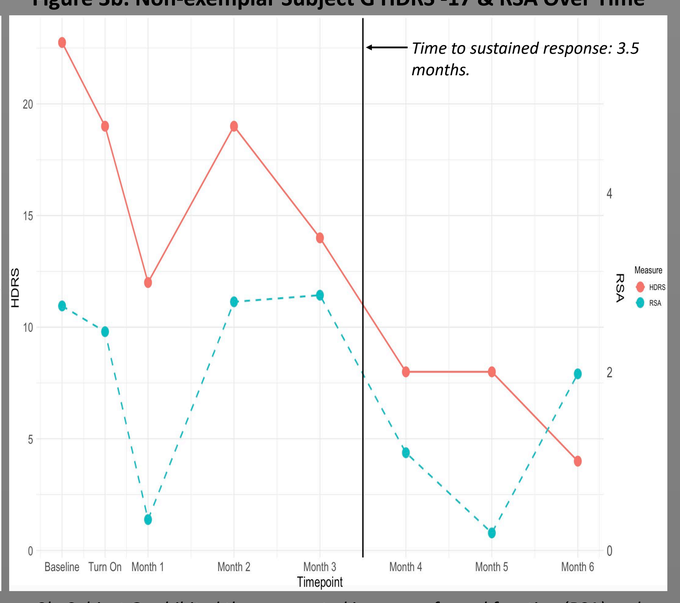

*2b. Subjects exhibited the expected increase of vagal function (RSA) and decrease of symptom severity (HDRS) across time. Pearsons r= -.49, t(7) = -1.3817, p = .2163.*

**Figure 3a. Exemplar Subject B HDRS -17 & RSA Over Time**



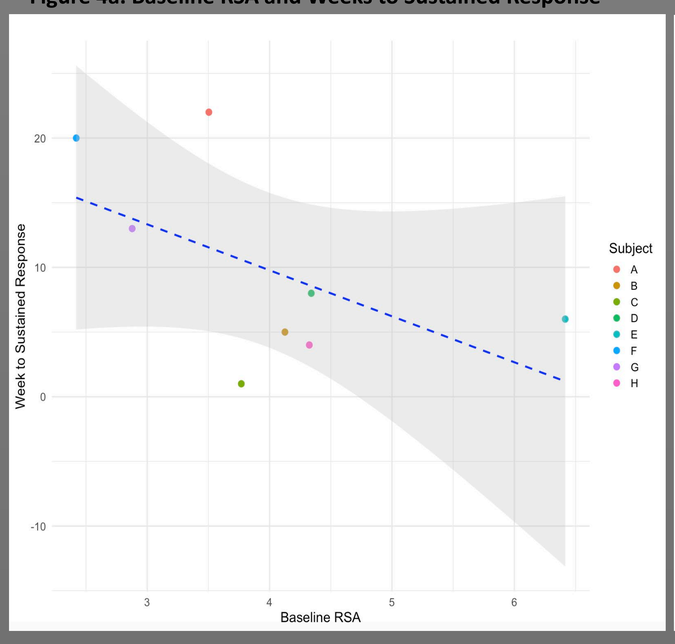

*3a. Subject B exhibited the expected increase of vagal function (RSA) and decrease of symptom severity (HDRS) across time. Pearsons r= -.49, t(7)= -1.3817, p = .2163.*

**Figure 3b. Non-exemplar Subject G HDRS -17 & RSA Over Time**



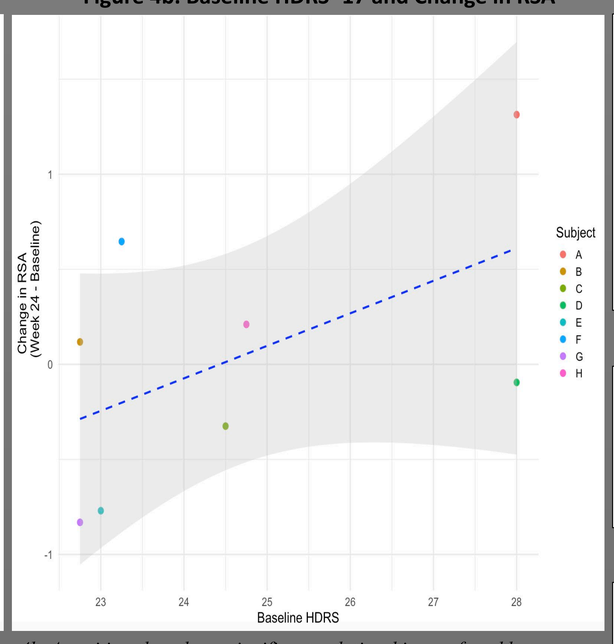

*3b. Subject G exhibited the unexpected increase of vagal function (RSA) and decrease of symptom severity (HDRS) across time. Pearsons r= .618, t(7) = 1.929, p = .1019*

**Figure 4a. Baseline RSA and Weeks to Sustained Response**




*4a. A negative, though nonsignificant relationship was found between baseline RSA and weeks to a sustained response (Spearman: -.55, p = .153).*

**Figure 4b. Baseline HDRS -17 and Change in RSA**




*4b. A positive, though nonsignificant, relationship was found between baseline HDRS 17 and change in RSA (Week 24 – Baseline) (Spearman: .529, p=.1).*

## FINDINGS

1) Depression severity significantly decreased across SCC DBS treatment.
2) Treatment Resistant Depression cohort had baseline HRV below typical depression range with high variance.
3) Cardiac vagal control demonstrated variable pattern over six months of SCC DBS. RSA increased in five subjects and decreased in three subjects.
4) Greater baseline RSA may lead to fewer weeks to sustained response, and greater baseline symptom severity may predict greater increase in RSA across time.

## IMPLICATIONS

Aberrant vagal activity may be a viable marker for subject selection to predict treatment success in future SCC DBS trials. We further elucidate the role of the subgenual cingulate cortex in affective and autonomic states. Enhanced vagal function may be a mechanism in the efficacy of SCC DBS in individuals who do not respond to conventional treatments like medication and psychotherapy.

## FUTURE DIRECTIONS

Continue to acquire more data to increase statistical power. Record HRV from both excluded and included subjects in upcoming SCC DBS clinical trials to assess autonomic activity in relation to psychiatrist judgment.

Link for poster reprint: https://psychophyslab.arizona.edu/conference-presentations

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