What is the role of autonomic activity in the treatment of depression with subcallosal cingulate deep brain stimulation?

Jacob Dahill-Fuchel[1], John JB Allen[1], Elisa Xu[2], Jacqueline Overton[2], Chris Rozell[4], Patricio Riva-Posse[3], Helen Mayberg[2], Allison Waters[2]

1. University of Arizona, Department of Psychology, 2. Icahn School of Medicine at Mount Sinai, Nash Family Center for Advanced Circuit Therapeutics, 3. Emory University School of Medicine, Department of Psychiatry, 4. Georgia Institute of Technology

Digital Copy of Poster
https://jallen.faculty.arizona.edu/content/conference-presentations

BACKGROUND

Major Depressive Disorder is associated with aberrant autonomic function as determined by cardiac vagal control 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 produced clinical benefit in patients with treatment resistant depression as determined by a decrease in Hamilton Depression Rating Scale (HDRS-17).

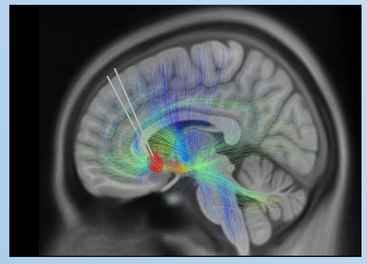
The SCC is part of the central autonomic network, which is involved in vagal function and cardiac regulation (Lane et al., 2013[3]; Riva-Posse & Mayberg 2014[4]).

SCC DBS may impact autonomic function. We hypothesize an increase in HRV and a decrease in clinical symptoms with SCC DBS.

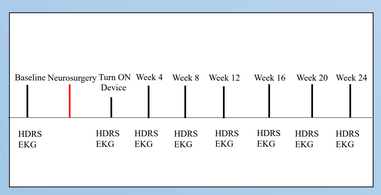
OBJECTIVES

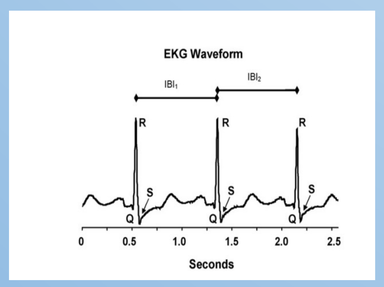
- Does SCC DBS have an effect on cardiac vagal control (HRV) and depressive symptoms (HDRS-17) across treatment?
- Does the magnitude of change in HRV and depressive symptom severity correlate across treatment?

METHODS



Alagapan, S., Choi, K.S., Heisig, S. *et al.* Cingulate dynamics track depression recovery with deep brain stimulation. *Nature* (2023). https://doi.org/10.1038/s41586-023-06541-3





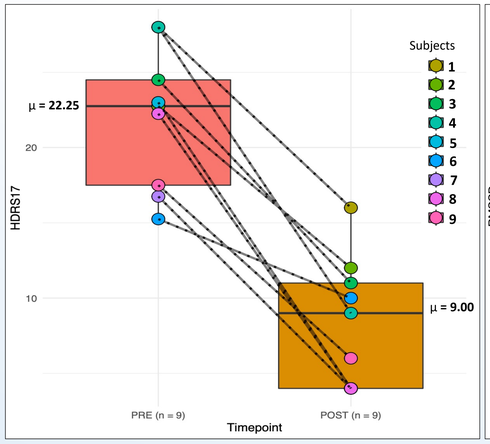
Subjects: Nine subjects with treatment – resistant major depressive disorder received neurosurgical implantation of two leads in the subcallosal cingulate cortex ; Clinical Trials ID: NCT01984710)

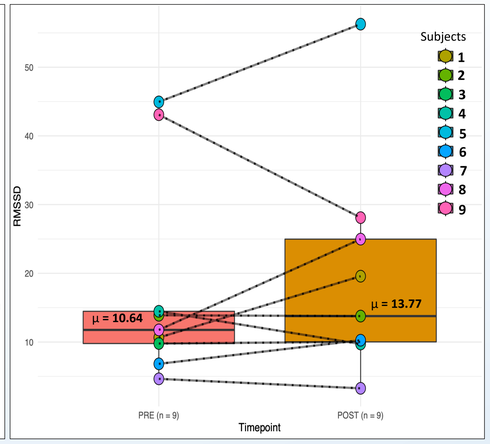
Procedure:
a. Monthly laboratory visits for 6 months.
b. Respiration and EKG recorded at a rate of 1000 samples per second during each time point.
c. HDRS-17 acquired at each timepoint.
d. Conditions (3-5 minutes each):
   i. DBS ON, DBS OFF

EKG Preprocessing and HRV extraction
- Lowpass filter (50hz) applied to EKG.
- R-spikes identified and interbeat interval (IBI) series extracted in QRSTool[5].
- The root mean square of successive differences between adjacent r-spikes was calculated to reflect vagal influence on heart rate (RMSSD).

FIGURES

Figure 1: a. Change in Symptoms Over Time (HDRS-17) b. Change in RMSSD Over Time (RMSSD)

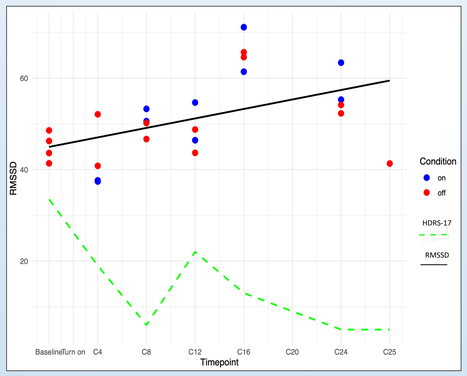


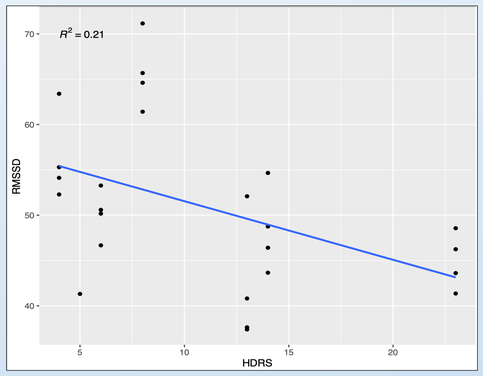


1a. Subjects exhibited a significant decrease in HDRS-17 from Baseline to Week 24 of SCC DBS *t(8) = 8.9417, **p<.001.*

1b. Subjects (stimulation off) did not exhibit a statistically significant difference in RMSSD from Baseline to Week 24 *t(8) = -0.6047, p = 0.5621.*

Figure 2: a. Exemplar Subject 5 HDRS and RMSSD across time b. Subject 5 Correlation of RMSSD & HRDS)

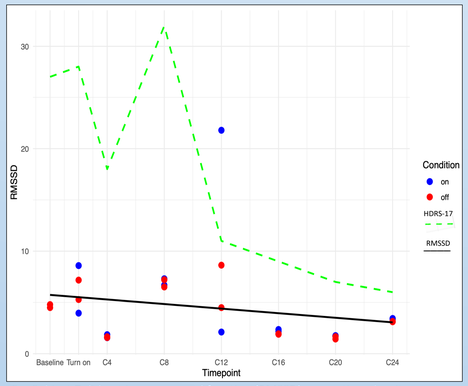


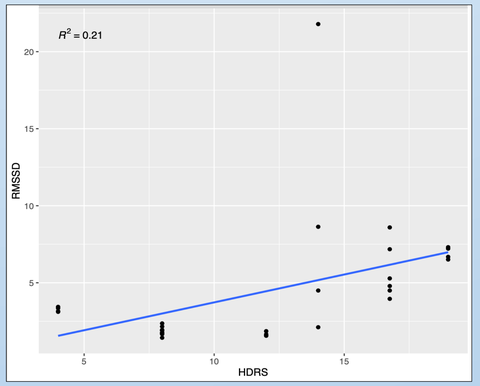


2a. Subject 5 exhibited the expected increase of vagal function (RMSSD) and decrease of symptom severity (HDRS) across time t(8) = -2.4938, p = .0202.

2b. Subject 5 exhibited a negative correlation between RMSSD and HDRS r = -.442.

Figure 3: a. Non-exemplar Subject 7 HDRS and RMSSD across treatment. b. Correlation of HDRS and RMSSD

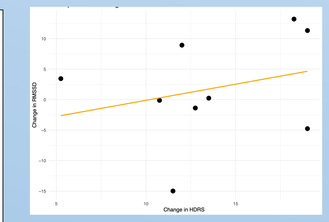


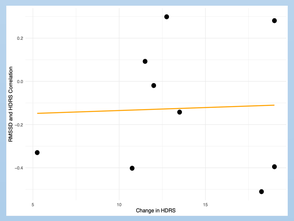


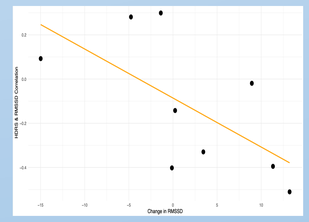
3a. Subject 7 did not increase vagal function (RMSSD) across time despite a decrease in symptom severity (HDRS) t(8) p = .232, r = .453.

3b. Subject 7 unexpectedly exhibited a positive correlation between RMSSD and HDRS r = .453.

Figure 4: Overall strength of relationship between HDRS and RMSSD over time for all subjects







Change in RMSSD did not predict change in HDRS t(7) - 0.7548, p = 0.475, r = .274.

Change in HDRS did not predict strength of vagal function and symptom severity correlation t(7) = 0.1088, p = 0.916, r = .041.

Change in RMSSD did not predict strength of vagal function and symptom severity correlation but showed a large effect size: t(7) = -2.1939, p = .06431, r = -0.638.

DEMOGRAPHICS

Patient ID casigni	Sex	Race	Age at study entry (yrs)	Medication* (Baseline, WK 24)	HDRS-17 (Baseline, WK 24)	DBS Therapeutic Dose Bilateral, 130 Hz, 90μs (Baseline, WK 24)
01	F	White	56	3, 3	27, 10	3.5, 5.0
02	M	White	37	1, 1	23, 8	3.5, 4.5
03	F	White	44	2, 2	26, 4	3.5, 3.5
04	M	White	27	3, 3	21, 6	3.5, 4.5
05	F	White	32	5, 6	28, 16	4.5, 6.0
06	F	White	52	2, 2	23, 12	4.5, 5.0
07	M	White	26	4, 4	25, 11	4.5, 4.5
08	M	White	59	5, 7	28, 9	4.5, 4.5
09	F	White	34	6, 5	23, 5	4.5, 4.5

*Number of medications that may affect heart rate

FINDINGS

1) Depression severity decreased across SCC DBS treatment.

2) Cardiac vagal control demonstrated variable pattern across patients over six months of SCC DBS. HRV increased in five patients, decreased in two patients, and did not show a statistically significant change in two patients.

3) In this small sample, those patients with the largest increase in HRV had the predicted negative correlation with HRSD symptoms (p = .064, r = -.64). HRV was significantly negatively correlated with symptom severity in four patients, significantly positively correlated in three patients, and demonstrated no relationship in two patients.

IMPLICATIONS

Results further elucidate the role of the subgenual cingulate cortex in affective and autonomic states. SCC DBS may restore aberrant vagal function in patients with treatment resistant depression. 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

Investigate long-term effects of SCC DBS on autonomic adaptability and mood in depressed individuals.

Record ambulatory cardiac activity in naturalistic settings with ecological momentary assessment.

Optimize stimulation treatment parameters with real time heart rate variability biofeedback.

References

1. Bassett D. A literature review of heart rate variability in depressive and bipolar disorders. Aust N Z J Psychiatry. 2016 Jun;50(6):511-9. doi: 10.1177/0004867415622689. Epub 2015 Dec 23. PMID: 26698824.
2. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. Neuron. 2005 Mar 3;45(5):651-60. doi: 10.1016/j.neuron.2005.02.014. PMID: 15748841.
3. Lane RD, Weidenbacher H, Smith R, Fort C, Thayer JF, Allen JJ. Subgenual anterior cingulate cortex activity covariation with cardiac vagal control is altered in depression. J Affect Disord. 2013 Sep 5;150(2):565-70. doi: 10.1016/j.jad.2013.02.005. Epub 2013 Mar 7. PMID: 23473547.
4. Riva-Posse P, Choi KS, Holtzheimer PE, McIntyre CC, Gross RE, Chaturvedi A, Crowell AL, Garlow SJ, Rajendra JK, Mayberg HS. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2014 Dec 15;76(12):963-9. doi: 10.1016/j.biopsych.2014.03.029. Epub 2014 Apr 13. PMID: 24832866; PMCID: PMC4487804.
5. Allen, J.J.B., Chambers, A.S., & Towers, D.N. (2007). The many metrics of cardiac chronotropy: A pragmatic primer and a brief comparison of metrics. Biological Psychology, 74, 243–262. PMID:17070982