Magnetic Seizure Therapy in Treatment Resistant Depression

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Major Depressive Disorder Disease Burden

- Millions across the globe are affected annually
- Functional impairment equal to or surpassing that of chronic medical conditions
- Leading cause of disease burden world-wide
- Economic burden on society: 200 billion dollars per year

Mathers CD Loncar ,D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Medicine 2006;3(11):2011-2030.

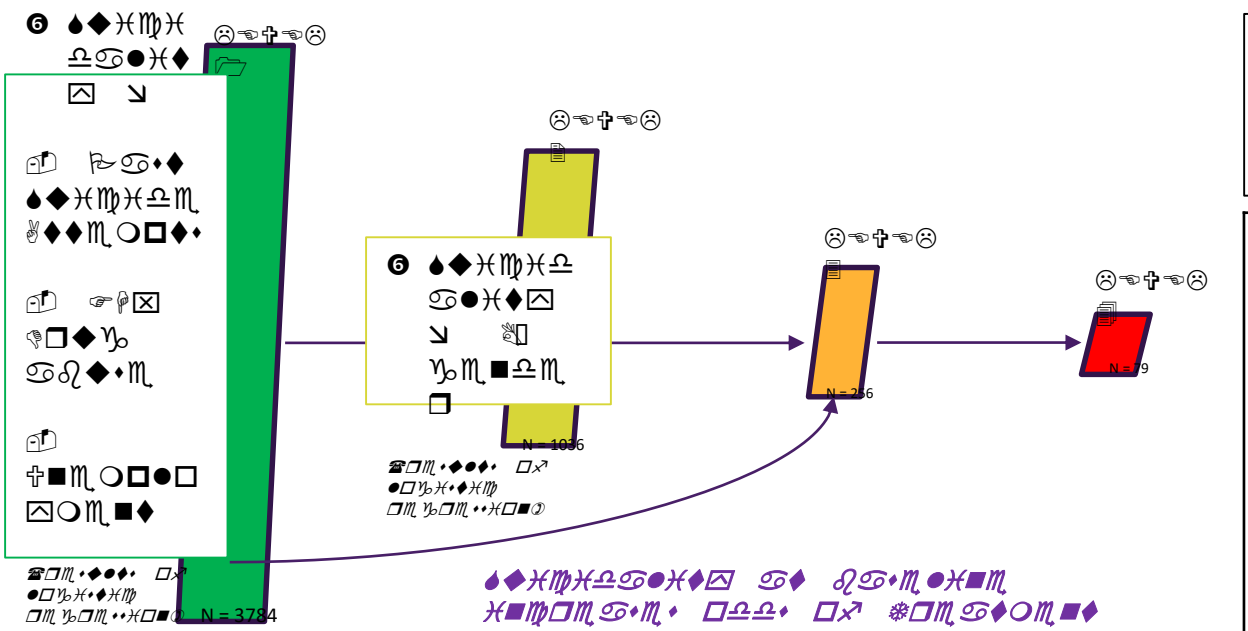
Sims BE, Nottlemann ,E, et al. Prevention of depression in children and adolescents. J Prev Med 2006;31(6S1).

Some Statistics on Resistant Depression

- 40-50 % patients with depression do not respond (i.e., <50 % reduction) to medication (Triverdi et al 2006)
- Remission was about 33 percent in STAR*D (Trivedi et. al 2006)
- These patients are twice as likely to be hospitalized
- Receive up to 3 times more psychiatric medications
- 19 times the mean total medical costs of non-treatment-resistant depression
- For remitters up to 40 % relapse at 2 years (Bolland and Keller, 2009)

Major Depressive Disorder Suicide

- Mental illness can cut 10 to 20 years from a person's life expectancy.
- Nearly 40,000 Americans die by suicide each year – an average of more than 100 suicides a day.
- More than half of suicides involve people 45 and older.
- The World Health Organization (WHO) reports that: In the last 45 years suicide rates have increased by 60% worldwide.
- After accidents, suicide is the second leading cause of death among those aged 15-34 (male and female).



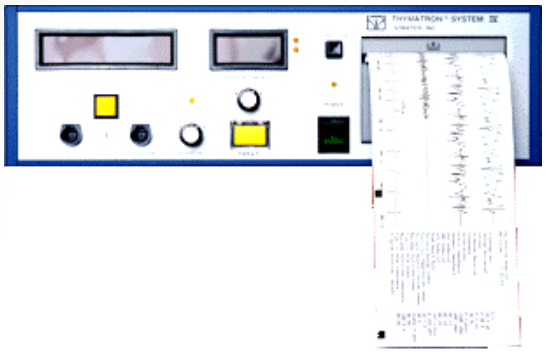
3 SUICIDE
0 Absent.
1 Feels life is not worth living.
2 Wishes he/she were dead or any thoughts of possible death to self.
3 Ideas or gestures of suicide.
4 Attempts at suicide (any serious attempt rate 4).

△= 0.29 (p<0.001) △= 0.26 (p<0.001) △= 0.16 (p<0.01) △= 0.18 (p>0.01)

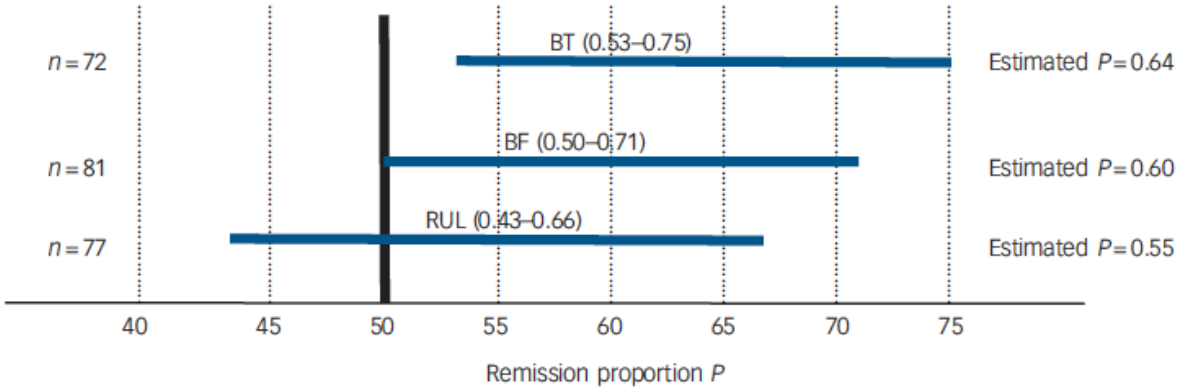
time (change score as per suicide item of HRSD)

Weissman et al. NPP 2021

One of the most effective treatments in medicine……..



- Remission (i.e., no Depression): 60-80 percent
- Remission i.e., no suicidality: >80 percent



Kellner, C. H. et al.. (2010). Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *The British Journal of Psychiatry, 196*(3) 226-234.

Controversies

- Common Side effects: disorientation, retrograde and anterograde amnesia
- Uncommon: cardiac arrest, stroke, aspiration, prolonged seizures, fractures, malignant hyperthermia, death (1/10,000)

Only 1% of patients with resistant depression receive ECT– **fear, stigma, cognitive side effects**

Magnetic Seizure Therapy (MST)

- ECT side effects: shunting of electrical activity and higher energies
- MST involves no shunting: minimal involvement of brain structures related to memory
- Pulse width of MST is closer physiologically to activate neurons

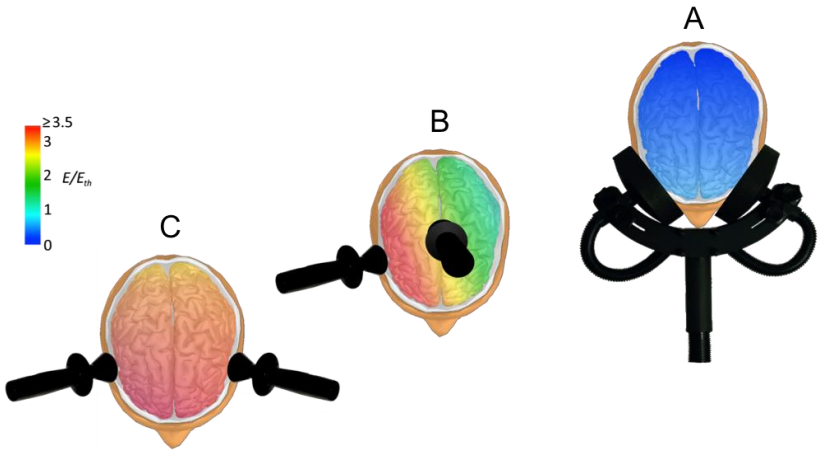
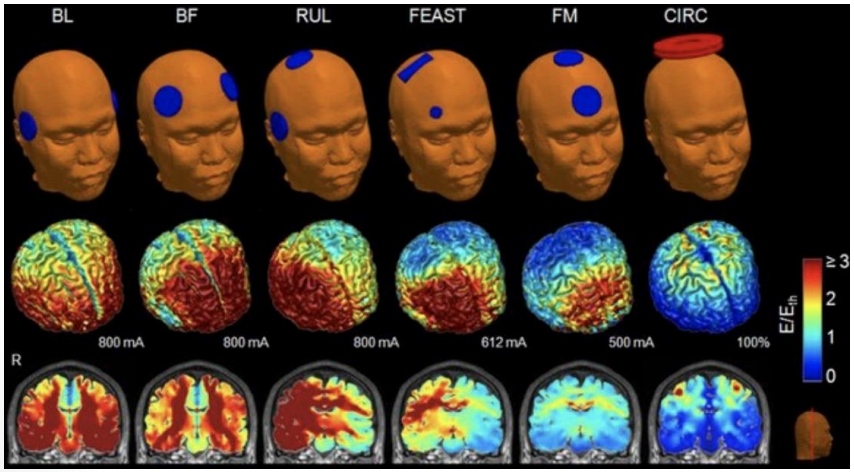


Figure 1. This figure demonstrates that (A) MST produces a seizure with much lower e-field strength (cooler colors) compared to (B) right unilateral ECT or (C) bilateral ECT which requires much higher e-field strength (hot colors) to produce an adequate seizure. Additionally, the skull shunts the electrical field making the electrical field from ECT largely non-focal. It is postulated that more focality and lower e-field strength contributes to the preservation of cognitive performance of MST compared to ECT. Modified from Fig 3, Deng et al. 2011.

ECT vs MST

	ECT	MST
Pulse Duration	Ultra-brief (i.e., 0.3-0.4 msec), standard (1 msec)	Ultra-brief (0.3 msec)
Method of seizure induction	Electric	Magnetic
Target location	Bifrontal, bitemporal, right unilateral	Frontal, vertex
Localization	Non-focal due to skull shunting and volume conduction	Focal



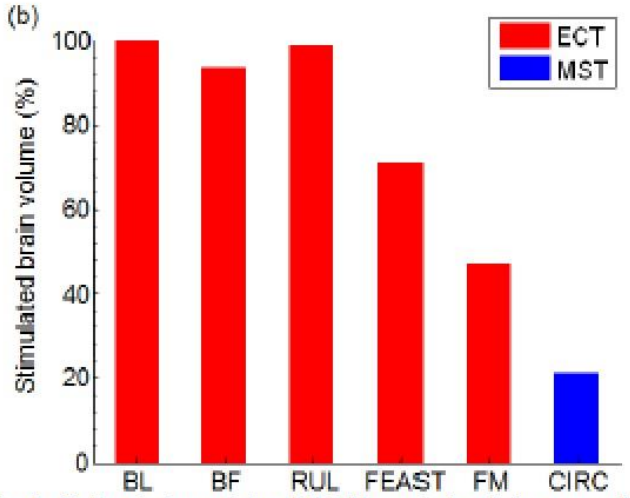
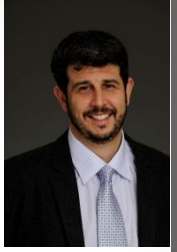


Fig. 2. (a) Descriptive statistics of E-field magnitude relative to neural activation threshold at current of 800 mA for BL, BF, and RUL ECT, 612 mA for FEAST, 500 mA for FM ECT, and 100% stimulator output for CIRC MST coil configuration. Boxes indicate the interquartile range (25th to 75th percentile) with the median marked by a horizontal black line. Whiskers delimit approximately the 99.3 percentile of the E-field distribution. Outliers beyond this range are plotted in green. (b) Percentage brain volume stimulated above neural activation threshold ($E \geq E_{th}$).

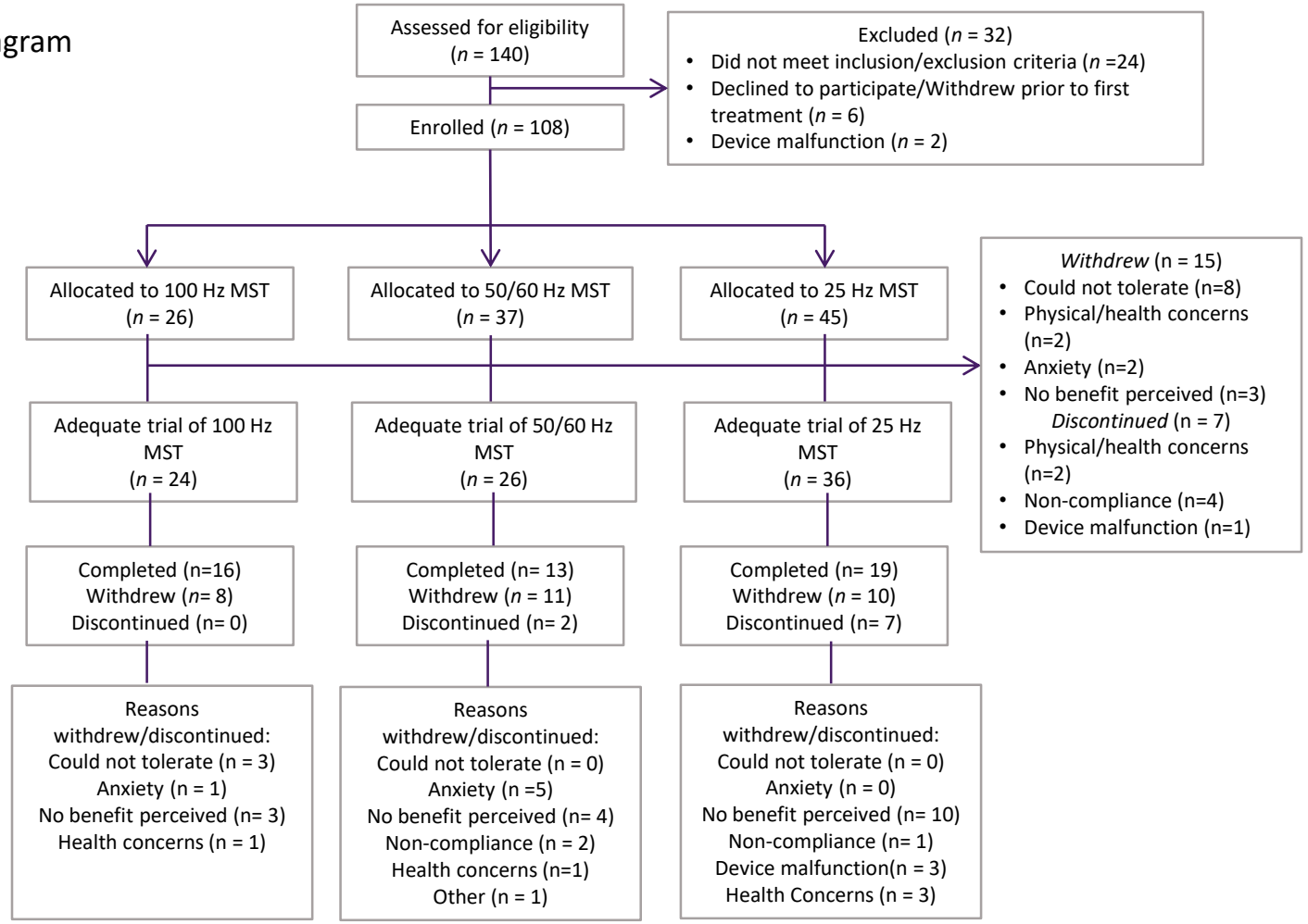
Lee et al. 2014 IEEE

CAMH Study



- Pilot study of Frontal MST at 3 different stimulation frequencies
  - 100 Hz, 60Hz, 50 Hz and 25 Hz
  - Treatment studies in humans have used 100 Hz, in primates 22 Hz shown to be associated with optimal seizure production
- Patients treated in an open label manner
  - Primary DVs of interest included remission and response rates:
    - In pts completing more than 3 treatments
    - In completers (i.e., completed the protocol with target of either remission or 24 treatments)
  - Cognition evaluated at baseline an at the end of treatment
  - Neurophysiology used as a predictor of treatment response
- Neurophysiology included TMS combined with EEG to measure cortical inhibition from the DLPFC in patients with TRD

Consort Diagram



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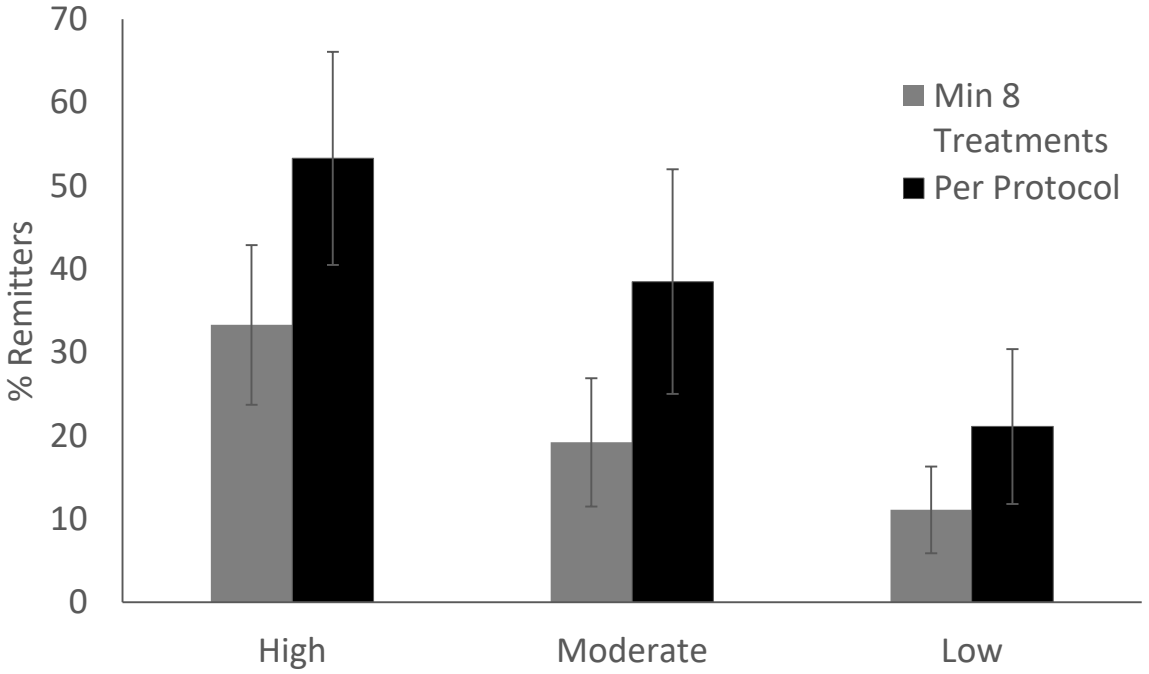
MST TRD Remission



Daskalakis et al. 2020 NPP

Cognitive Outcomes

Means and SD Across Groups for Neurocognitive Measures among patients who have completed an adequate trial of MST (≥ eight treatments) or per protocol.

	Adequate Trial			Per Protocol		
	Pre	Post		Pre	Post	
Measure	M (SD)	M (SD)	*t*	M (SD)	M (SD)	*t*
MoCA	25.73 (3.63)	25.96 (3.5)	-0.635	25.88 (3.78)	26.02 (3.06)	-0.504
AMI - SF	51.42 (6.89)	41.58 (8.61)	17.56*	51.16 (7.4)	40.98 (9.1)	12.875*
Trails A	40 (33.3)	34.05 (14.27)	1.183	40.4 (31.52)	36.38 (15.94)	0.076
Trails B	95.11 (67.89)	84.88 (48.48)	-0.173	93.21 (66.49)	90.64 (56.14)	-0.369
Symbol Coding	50.68 (13.6)	51.09 (13.44)	0.866	50.75 (13.66)	49.05 (12.26)	1.783
HVLT-R Total	25.26 (6.29)	24.67 (5.2)	2.059	25.53 (6.64)	24.32 (5.5)	2.399
HVLT-R Recall	8.78 (2.93)	8.53 (3)	1.661	8.93 (3)	8.34 (3.33)	2.233
HVLT-R Recognition Index	10.53 (1.93)	10.73 (1.66)	-0.571	10.8 (1.53)	10.57 (1.82)	1.277
Spatial Span Forward	8.47 (2)	8.58 (1.99)	0.177	8.53 (1.85)	8.41 (1.92)	0.561
Spatial Span Back	7.78 (2.06)	7.93 (1.99)	0.575	7.76 (1.92)	7.41 (1.93)	1.677
Spatial Span Total	16.24 (3.64)	16.51 (3.54)	0.454	16.29 (3.22)	15.82 (3.45)	1.38
LNS Total	15 (3.85)	14.99 (3.82)	0.872	15.2 (3.73)	14.77 (4.09)	1.275
Mazes Total Score	14.33 (7.91)	15.09 (8.62)	-0.451	12.84 (7.55)	13.02 (8.26)	-0.087
BVMT-R Total	21.8 (8.78)	25.39 (7.41)	-3.923*	22.6 (8.29)	25.1 (7.73)	-2.709
BVMT-R Learning	3.94 (2.16)	3.96 (2.23)	0.307	3.84 (2.26)	4 (2.18)	-0.282
BVMT-R Recall	8.4 (3.05)	9.85 (2.49)	-4.318*	8.65 (2.84)	9.6 (2.59)	-2.506
BVMT-R Recognition Index	5.58 (0.81)	5.81 (0.49)	-2.114	5.58 (0.73)	5.83 (0.44)	-1.939
COWAT Total	39.06 (14.55)	37.47 (14.36)	1.458	39.58 (16.2)	37.1 (15.49)	2.315
Categories Total	54.63 (19.4)	51.14 (20.66)	2.69	55.35 (20.89)	53.07 (20.15)	2.4
Stroop Color-Word Score	95.19 (22.25)	95.8 (22.02)	0.493	95.19 (22.02)	94.63 (22.92)	0.299
Stroop Color-Word Time (sec)	113.62 (16.23)	111.09 (17.92)	2.282	115.4 (17.85)	115.8 (17.3)	0.407

* $p < 0.005$

Note. MoCA = Montreal Cognitive Assessment; AMI – SF = Autobiographical Memory Interview-Short Form; Trails A/B = Trail Making Test, Part A or B; HVLT-R = Hopkins Verbal Learning Test-Revised; LNS = Letter Number Span; BVMT-R = Brief Visuospatial Memory Test-Revised; COWAT = Controlled Oral Word Association Test; Categories = Category Fluency Test.

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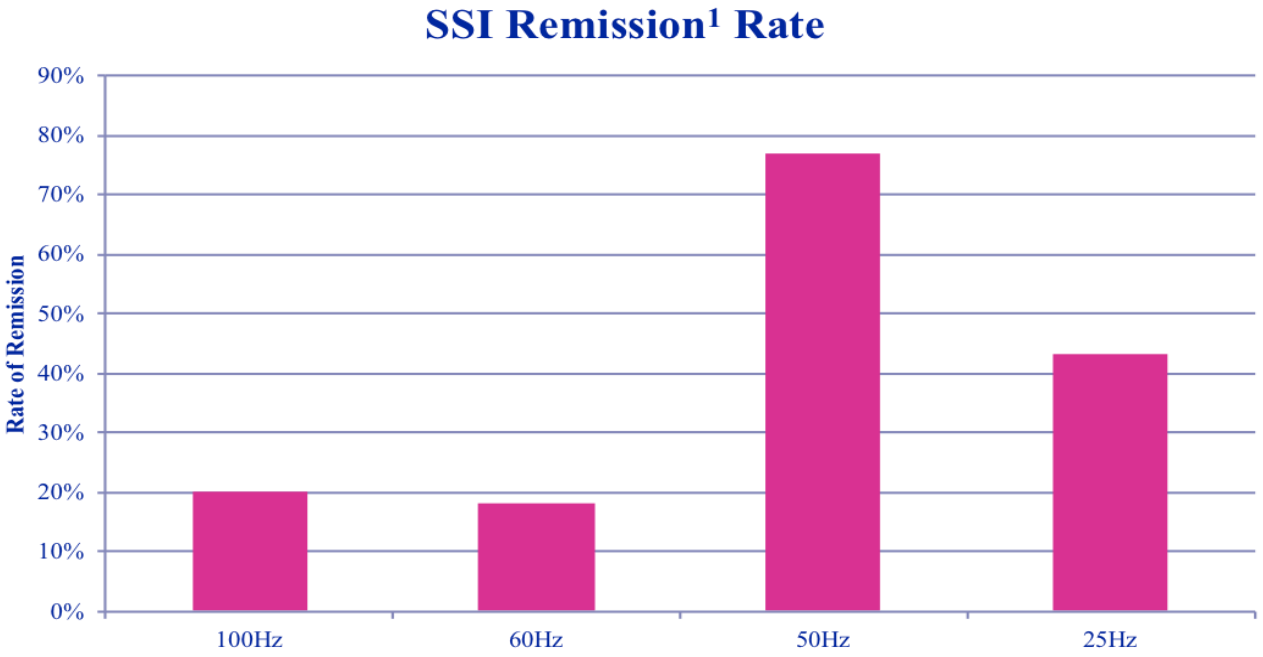
SSI Efficacy Rates

- Modified Intent-to-Treat (ITT) sample: minimum 8 treatments completed



Chi – square tests revealed the following significant differences:
50 Hz > 100 Hz: $\chi(1) = 7.80$, $p = .005$
50 Hz > 60 Hz: $\chi(1) = 6.81$, $p = .009$

[1]Remission = score of 0 at post-treatment SSI (i.e. no suicidal ideation reported)

Weissman et al. 2020 JAMA Open

Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy of Depression (CREST – MST)

- 5 year NIMH funded multi-center trial at UT Southwestern and the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada
- Target *n*= 260
- Target population = severe and/or treatment-resistant MDD (unipolar, w/o psychotic features)
- Design = randomized, double blind, parallel-group clinical trial with two treatment arms: Magnetic Seizure Therapy (MST) or right unilateral ultrabrief pulse electroconvulsive therapy (RUL-UB-ECT)

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CLINICAL TRIAL ARTICLE Provisionally accepted The full-text will be published soon. Notify me

Front. Psychiatry | doi: 10.3389/fpsyt.2017.00310

Magnetic seizure therapy in treatment resistant schizophrenia: A pilot study

 Victor M. Tang[1, 2], Daniel M. Blumberger[1, 2, 3, 4], Shawn M. McClintock[5, 6], Tyler S. Kaster[1, 2], Tarek K. Rajji[1, 2, 3, 4],  Jonathan Downar[1, 4, 7, 8], Paul B. Fitzgerald[9] and  Zafiris J. Daskalakis[1, 2, 3, 4*]

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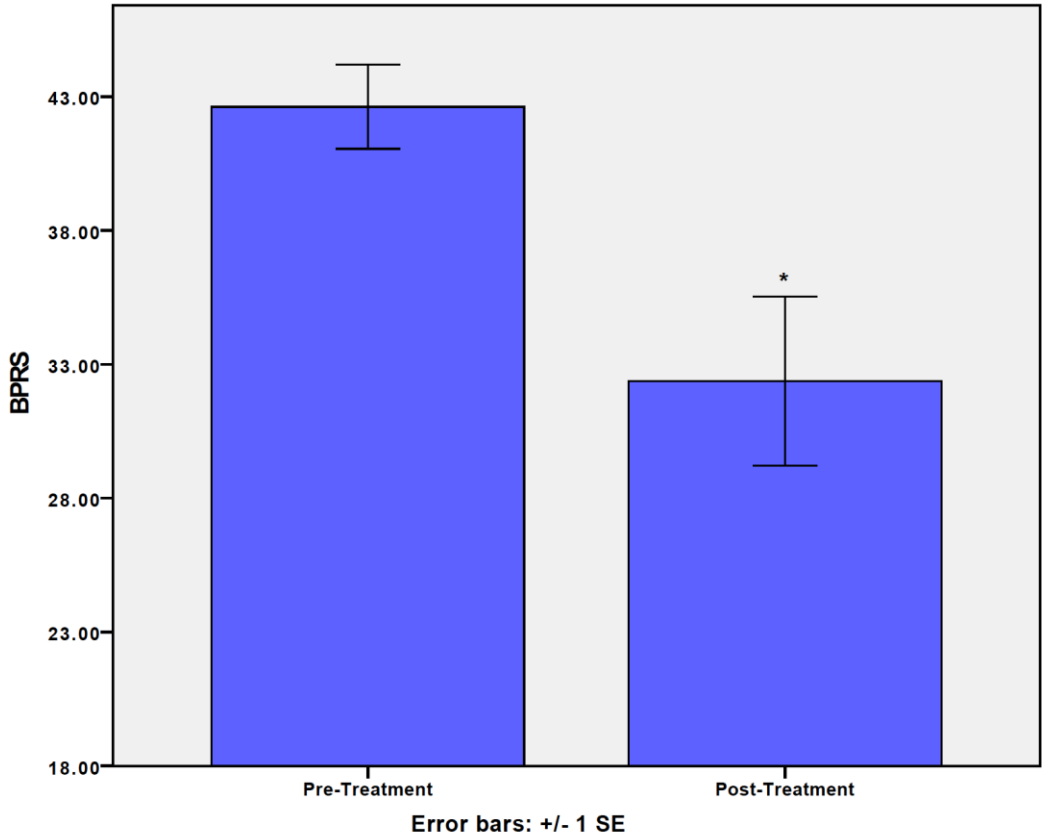
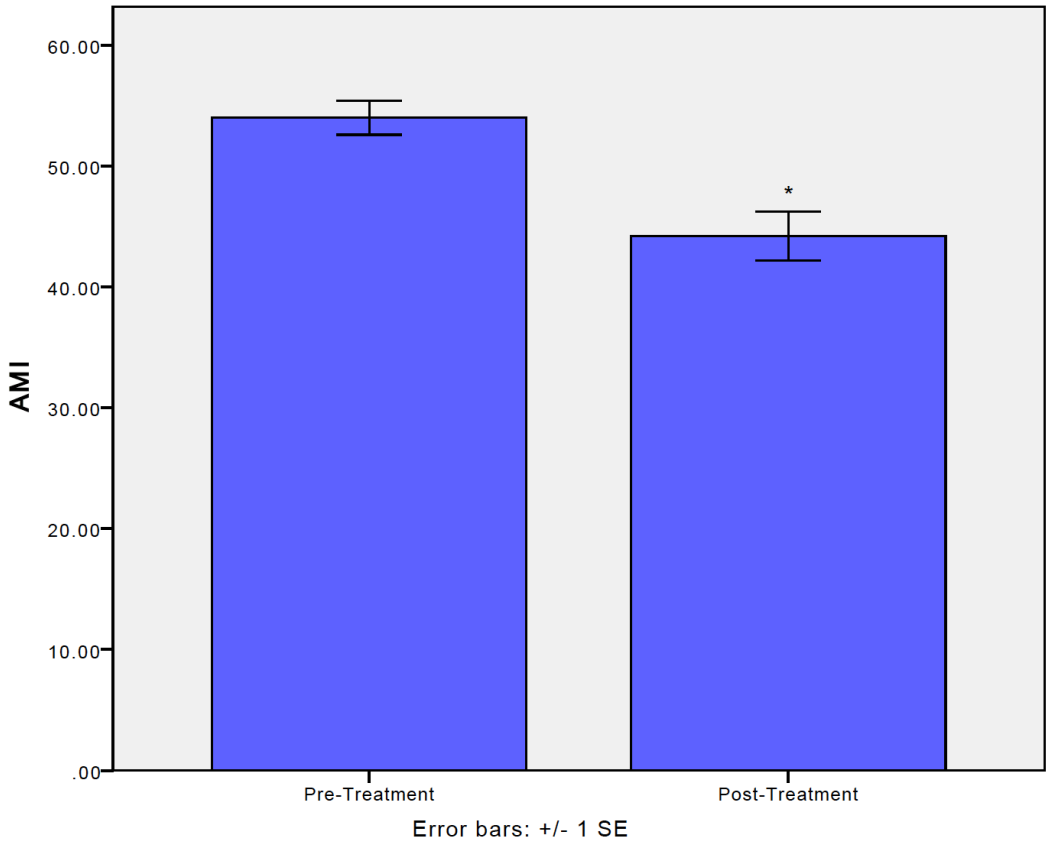
[7]Krembil Research Institute, University Health Network, Canada
[8]MRI-Guided rTMS Clinic, University Health Network, Canada
[9]Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University, Australia

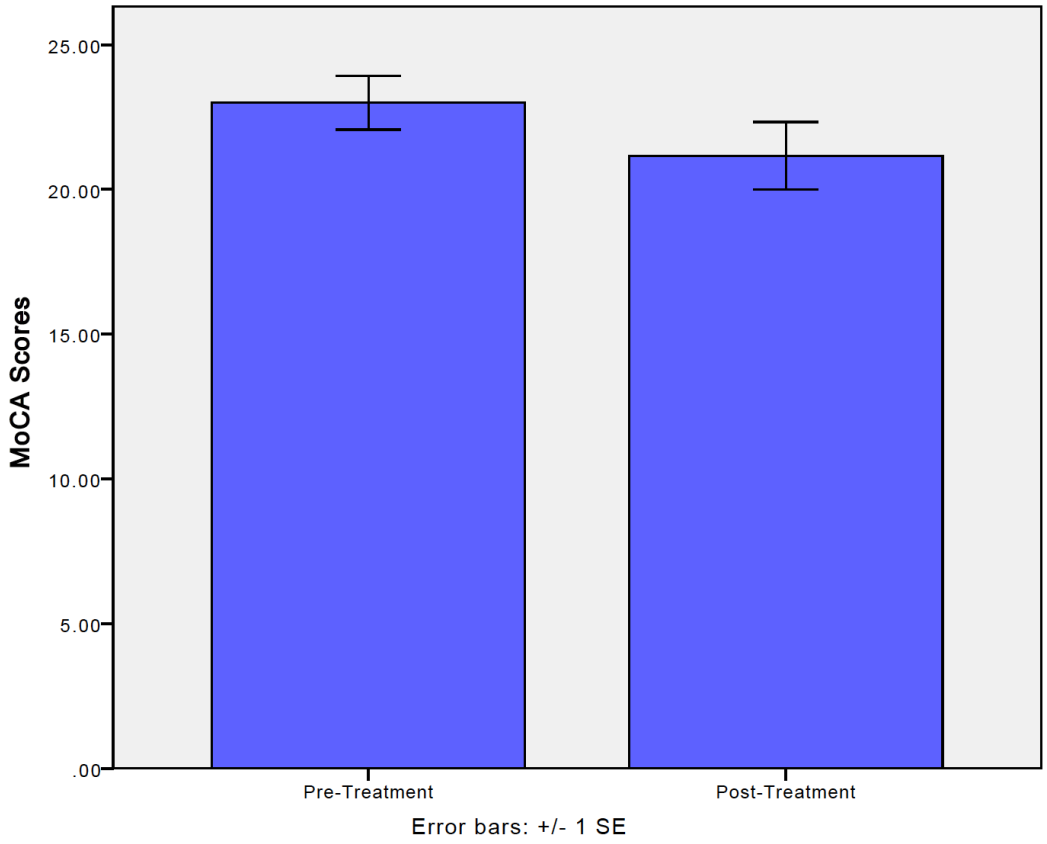
BPRS: All Subjects



Autobiographical Memory AMI



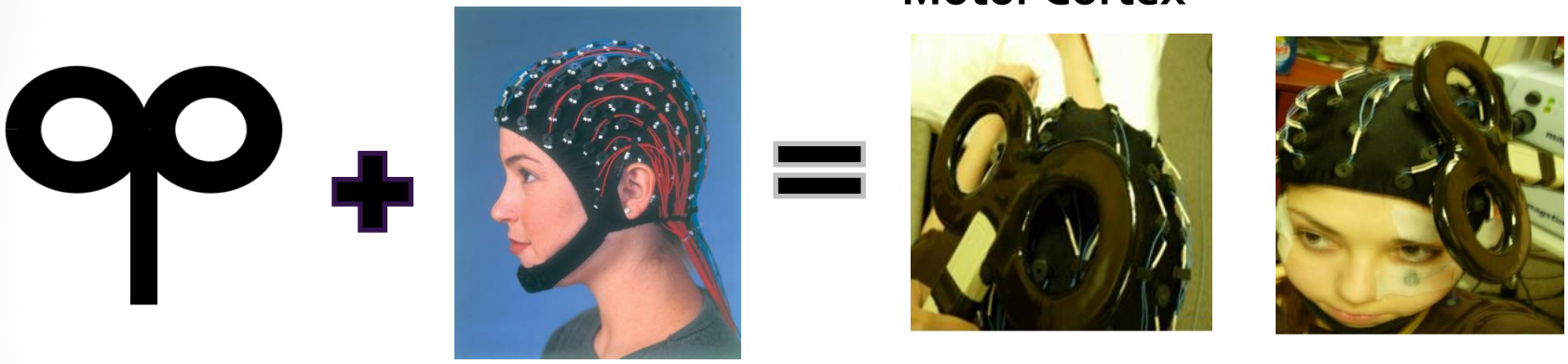
Cognition - MoCA



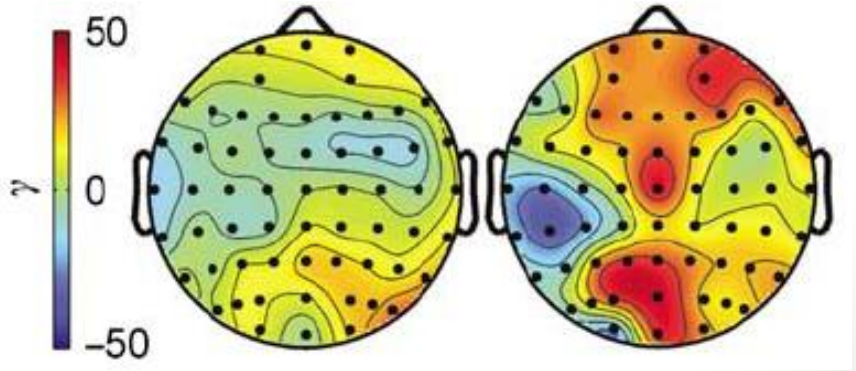
Magnetic Seizure Therapy for Schizophrenia (MAST)-Trial

- 5 year CIHR funded multi-center trial at CAMH, UBC and LHSC
- Target *n*= 160
- Target population = severe and/or treatment-resistant SCZ (unipolar, w/o psychotic features)
- Design = randomized, double blind, parallel-group clinical trial with two treatment arms: Magnetic Seizure Therapy (MST) or bilateral electroconvulsive therapy

Neurophysiology



Demonstrated inhibition/plasticity in DLPFC in healthy subjects

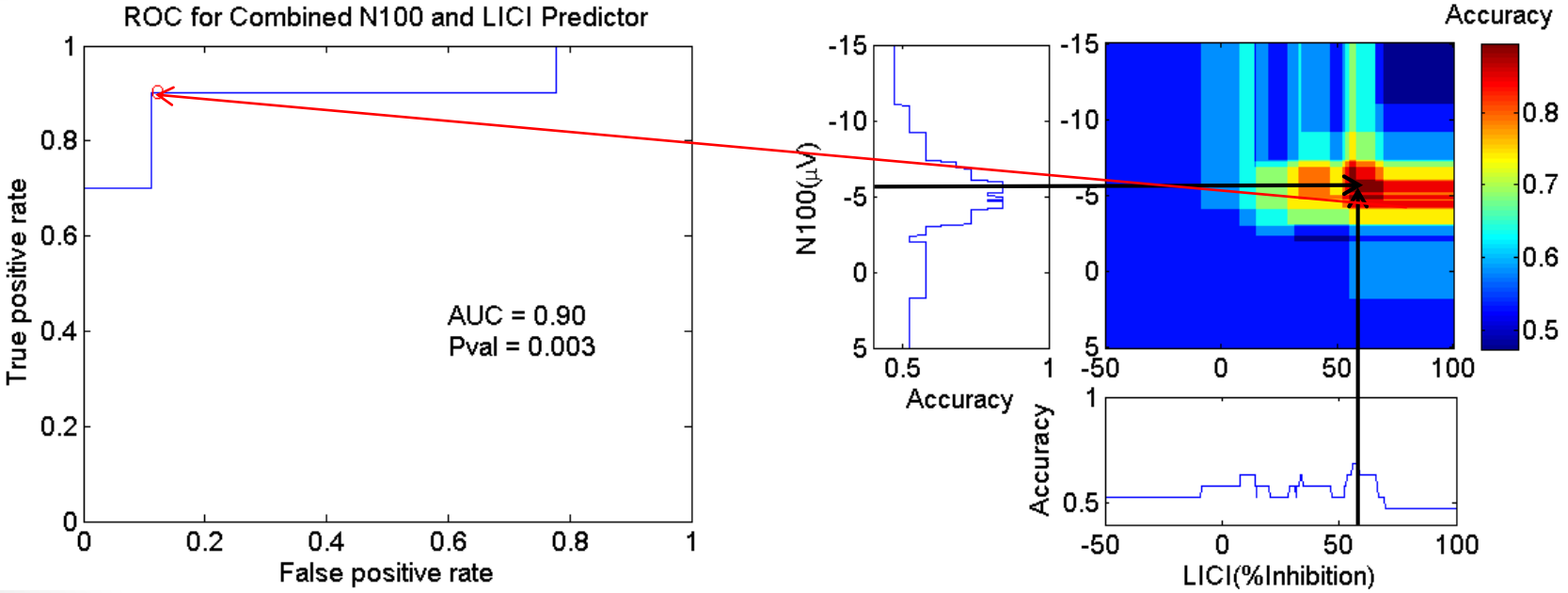


DLPFC: Combined Baseline N100 and LICI Predicts SSI Remission

Classifier:
Baseline N100 and LICI Value

Binary Outcome:
Post SSI = 0 → Remitter
Post SSI > 0 → Non-Remitter

Model: Subjects with baseline N100 less than cutoff or LICI greater than cutoff are classified as remitters



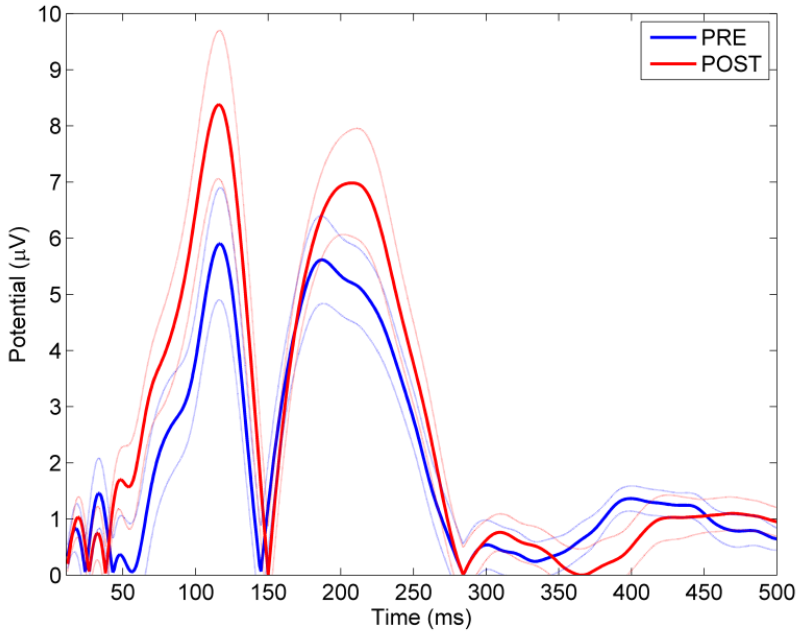
Accuracy for optimal cutoff: 89%

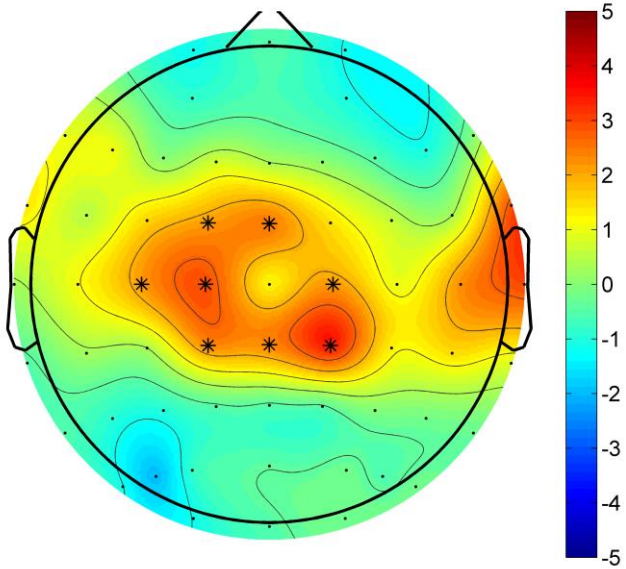
90% sensitivity and 89% specificity

Sun et al. JAMA Psychiatry 2016

MST-Induced Potentiation of Neural Plasticity

FCz



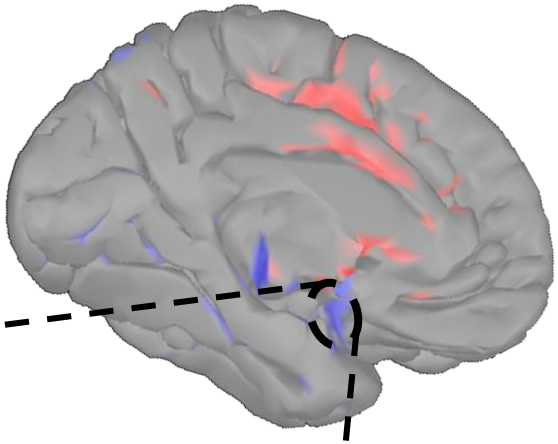


CEA_{theta} Post - Pre (T-score)

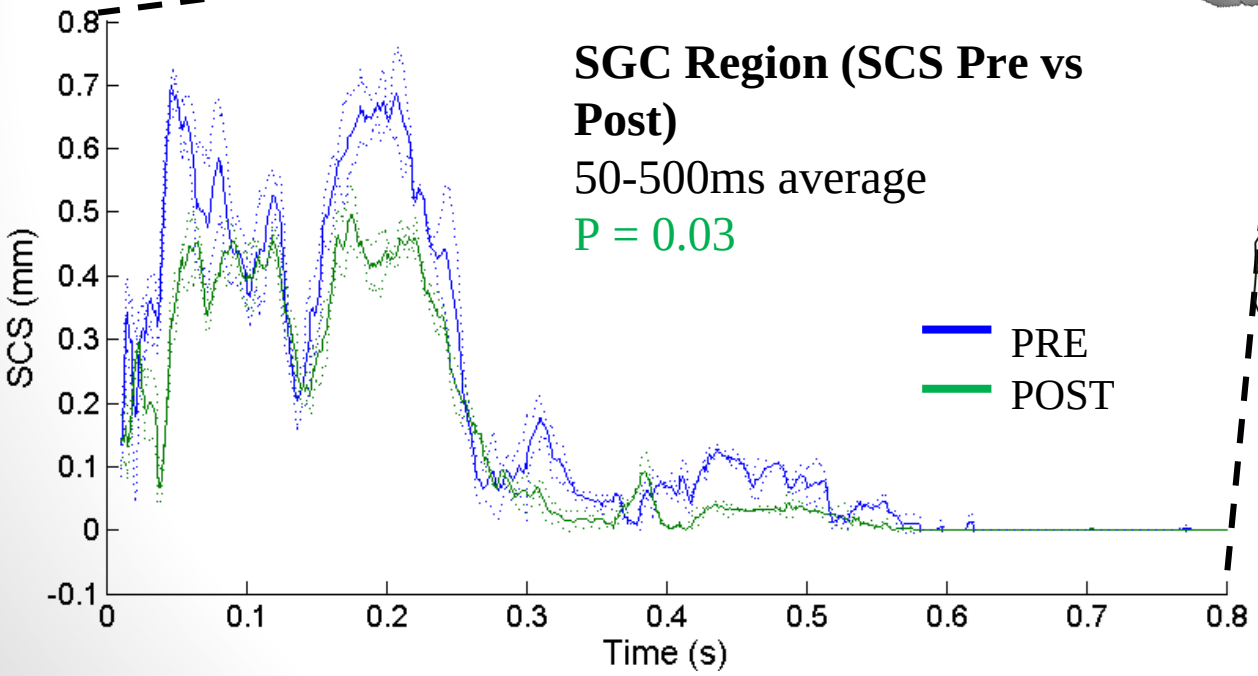
Sun et al. Translational Psychiatry, 2018 Nov 23;8(1):253

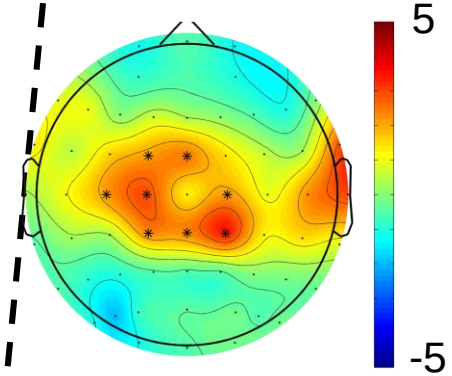
MST-induced decreased SGC Hyperactivity

Brain Source Image (Post-Pre T-score)
50-500ms average
P < 0.1 Threshold



SGC Region (SCS Pre vs Post)
50-500ms average
P = 0.03





Concurrent EEG (Post-Pre T-score)
50-500ms average
* Significant electrodes

Hadas et al, Translational Psychiatry

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