Single session of rTMS enhances brain metastability and intrinsic ignition

Rose Dawn Bharath[1]*, Sujas Bhardwaj[1,2,§], Rajanikant Panda[4,5,§], Albert Stezin[2,6,7], Sunil Kumar Khokhar[1], Shweta Prasad[2,5], Vidhi Tyagi[8], Nitish Kamble[2], Keshav Kumar[8], Netravathi M[2], Ravi Yadav[2], Jitka Annen[4,5], Kaviraja Udupa[9], Rajan Kashyap[1], Steven Laureys[4,5], Gustavo Deco[10], Pramod Kumar Pal[2]

[1]Neuroimaging and Interventional Radiology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India.
[2]Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India.
[4]Coma Science Group, GIGA-Consciousness, University of Liège, Belgium
[5]Centre du Cerveau[2], University Hospital of Liège, Belgium
[6]Clinical Neurosciences, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India.
[7]Centre for Brain Research, Indian Institute of Science, Bengaluru, India.
[8]Clinical Psychology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India.
[9]Neurophysiology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India.
[10]Center for Brain and Cognition, Computational Neuroscience Group, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Roc Boronat 138, Barcelona, 08018, Spain.

***Corresponding Author:**
Dr. Rose Dawn Bharath, Professor, Neuroimaging and Interventional Radiology, NIMHANS, Bengaluru-29, India. [Contact: +91-94808-29-651 cns.researchers@gmail.com ; drrosedawnbharath@gmail.com]

[§]Equally contributed to the manuscript

Abstract:

Background: Emerging evidence support the view that brain stimulation might improve essential tremor (ET) by altering brain dynamics and facilitating brain plasticity. Yet, we are still missing a mechanistic explanation of the whole brain dynamics underlying these plasticity defining changes. **Method:** In this study, we explored the effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) over primary motor cortex (M1) on dynamic functional connectivity (DFC) in patients with ET. Resting state fMRI (RsfMRI) was acquired before and after a single session of rTMS in 30 patients with ET and compared with RsfMRI of 20 age, gender and education matched healthy controls (HCs). We have measured the effect of brain stimulation using network topological re-organization through whole brain integration and segregation, brain stability and capacity of neural propagation through metastability and intrinsic ignition. **Results:** Patients with ET had altered DFC measures compared to controls. After a single session rTMS, the connectivity measures approached normality and patients with ET revealed significantly higher integration, lower segregation with higher metastability and increased intrinsic ignition. **Conclusion:** Brain metastability and intrinsic ignition measures could be valuable tools in appreciating mechanisms of brain stimulation in ET and other neurological diseases.

1. Introduction:

Neurological disorders are characterized by several disabling symptoms for which effective, mechanism-based treatments remain elusive and more advanced non-invasive therapeutic methods are being explored. Repetitive transcranial magnetic stimulation (rTMS) is a widely used classical non-invasive brain stimulation (NIBS) method which has been quite useful in management of drug resistant psychiatric disorders such as depression [1-4], mood disorders [5, 6], obsessive compulsive disorder [7-10], posttraumatic stress disorder (PTSD) [11-13] etc. These studies present mixed results in improvement of patient symptoms or clinical scores. Over the last three decades, TMS has helped us in understanding pathophysiology of many neurological disorders. TMS studies in essential tremor (ET), the most common tremor syndrome, have been helpful in demonstrating cerebello-thalamo-cortical circuitry (CTC) that is likely to be involved in the generation of tremor [14]. Pathophysiological insights into tremor syndromes have been supportive in selecting appropriate stimulation regions and rTMS parameters in the management of these diseases clinically [15].

Resting state fMRI (RsfMRI) methods in duplicate, before and after brain stimulation, is a popular method to assess the neurobiology of brain stimulation owing to its non-invasive nature, capability for whole brain analysis, better spatial resolution of deep-seated brain regions, ease of acquisition, repeatability and lack of any known adverse effects. Majority of the studies, using RsfMRI reveal a diffuse increased whole brain connectivity immediately after stimulation irrespective of the frequency of stimulation [16-19].Though some studies reveal decreased or no changes in connectivity [20-22], most of the studies have reported increased connectivity that extended beyond the stimulated region or networks [17, 23, 24]. This suggests that the effects of rTMS could either spread through anatomical tracts [25] or entrain brain oscillations increasing neural synchrony as a whole [26]. Stimulation of "task irrelevant" brain area like vertex [27] or sham stimulation revealed no changes in connectivity [28], reiterating the validity of this tool in measuring changes induced by rTMS. Another interesting point is that majority of studies report increased connectivity both after single session of rTMS and after rTMS therapy indicating the potential of using single session rTMS for research. One study [23] explored the network and found an increase in clustering coefficient and reduction in the path-length emphasizing enhancement in the small-world characteristic of network architecture after single session of rTMS. Recent

studies also indicate that these changes could be region specific, as the sensory cortex stimulation reveals different connectivity profile compared to motor cortex [29]. Homogeneous study groups, individualised target identification, uniform acquisition and analysis methods and longitudinal studies to measure sustainability of these changes are still required to completely decipher the connectivity changes encountered after rTMS.

In the brain connectivity community, brain function is increasingly seen as a result of metastable large scale network interactions [30]. Even at rest it is thought that one stable pattern of reverberating neural activity dynamically shifts from one stable state to another and hence it is postulated that brain is always in a multistable state [31]. Multistability is advantageous because, when faced with a stimulus, shifting equilibrium among coexisting states is more efficient than creating situation specific equilibrium afresh [32]. Dynamic functional connectivity (DFC) measures such as reproducible patterns of sliding window correlations, single-volume co-activation patterns, and repeating sequence of BOLD activity assume some degree of multistability. Recently it is proposed that neural propagation of local events to the entire network could be used to quantify the alteration of whole brain integrations as proposed in "Intrinsic Ignition" framework [33]. A high intrinsic ignition corresponds to rich and flexible brain dynamics having higher capacity to process event information, whereas low intrinsic ignition is poor, rigid network interaction with reduced neural communication [34]. In contrast to multi-stable approaches intrinsic ignition methods do not assume the presence of true points of equilibrium and appear instead as the result of opposing tendencies of the dynamics towards coupling and independence. There are several electrophysiological and behavioral studies that provide evidence that brain dynamics have features that are consistent with metastability [35-41].

Though significant imaging-based literature has accrued in the last couple of years revealing modulatory RsfMRI changes after single session of rTMS [42], to the best of our knowledge there are no previous literature on the effects of brain stimulation on the spatiotemporal dynamics and neural communication. We employ dynamic global functional connectivity assessments to test the hypothesis that the stimulatory effect of rTMS of M1 in ET might be caused by increases in neural propagation capacity, stability, and dynamic repertoire of the brain.

2. Method:

2.1 Participants: Thirty patients with ET [mean (age ± SD 37.33) ± 10.67 years, 6 Females] and twenty age, and education-matched HCs [mean (age ± SD) 38.2 ± 10.7 years, 4 Females] participated in this study after providing written informed consent. The study was approved by the institutional (NIMHANS, Bengaluru, India) ethics committee for humans. All participants were evaluated in detail by movement disorders specialists [(PKP, RY, NM, and NK); Supplementary Table 1]. All participants were right-handed and were checked for MRI and TMS contraindications. Subjects with ET were either on propranolol, primidone or clonazepam and these drugs were withheld prior to evaluation based on their half-life, i.e., at least 12 hours after the last dose of propranolol or primidone and 40 hours after the last dose of clonazepam. Secondary causes of tremors were primarily ruled out during clinical evaluation, and other causes, for instance hyperthyroidism where suspected was ruled out via blood investigations such as a thyroid profile. Participants with a structural lesion on MRI, prior brain, spinal or peripheral nerve trauma/surgery, claustrophobia and on neuroleptic drugs were excluded from the study. HCs with no neurological or psychiatric illnesses were recruited for MRI.

2.2 Experimental Design: Thirty patients of ET, diagnosed as per the consensus criteria of tremor [43, 44], and twenty, age and gender matched healthy controls were recruited from the neurology outpatient department at NIMHANS. The standard protocol followed for all patients of ET was as follows – informed written consent, clinical evaluation, estimation of resting motor threshold (RMT), resting state functional MRI siting 1 (RsfMRI-s1), rTMS, and a second resting state functional MRI siting 2 (RsfMRI-s2) within 10 minutes of the rTMS. HCs underwent only a single session of resting state functional MRI (RsfMRI) and did not undergo rTMS as ethical approval could not be obtained.

2.2.1 RsfMRI Data Acquisition: A 3T MRI scanner (Skyra; Siemens, Erlangen, Germany) was used for conducting this study. Data was collected between 2016-2019. The acquisition parameters were identical for RsfMRI-s1, RsfMRI-s2 in ET and for RsfMRI in HCs. To prevent head movement, sufficient padding and ear plugs were provided to all subjects. Whole brain Blood oxygen level dependent (BOLD) images were acquired using a spin echo sequence (TR = 2000 ms; TE = 20 ms; refocusing pulse

90°; 4.0 mm slice thickness in an inter-leaved manner with an FOV of 192 × 192 mm^2; matrix 64 × 64 voxels; voxel size 3 × 3 × 4 mm^3; 250 dynamics). A three-dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence was acquired (TR=1900 ms; TE=2.4 ms; voxel size 1×1×1 mm^3, slice thickness=1mm) for spatial registration and segmentation.

2.2.2 rTMS Parameters: After RsfMRI-s1, subjects were moved to another room adjacent to MRI, and rTMS was delivered using a Magstim Super Rapid stimulator (Magstim Co. Ltd, Whitland, UK) with a figure-of-eight coil configuration. rTMS was applied tangentially to the scalp with the handle pointing backward and laterally at an approximate angle of 45◦ to the mid-sagittal line, perpendicular to the presumed direction of the central sulcus. rTMS was delivered over the left primary motor cortex (M1) by delivering 900 stimuli at 90% of resting motor threshold (RMT) and 1 Hz for 15 min. The RMT was determined as the lowest intensity that produced motor evoked potentials of >50 μV in at least five out of 10 consecutive single-pulse TMS stimuli using same Magstim Super Rapid stimulator. The stimulator was attached to an electromyography machine from the right hand first dorsal interosseous muscle using Ag-AgCl surface electrodes placed over the muscle in a belly-tendon arrangement.

2.3 Data Analysis: RsfMRI data was recorded for 250 dynamics (~ 8.33 min), however, we removed first five dynamics from fMRI before pre-processing to avoid signal inhomogeneity during scanner start transition period.

2.3.1 RsfMRI data pre-processing: RsfMRI data pre-processing steps included realignment, segmentation of the structural data for regressing out the white matter and cerebrospinal fluid (CSF) effects, normalization to MNI152 standard space of 3 × 3 × 3 mm^3, and motion correction using Friston's 24-motion parameter [23]. Data was checked for head motion using the Artefact Detection Toolbox (ART) and found not being significantly different between RsfMRI-s1, RsfMRI-s2 and RsfMRI of HC. SPM12 was used for pre-processing of the fMRI data.

2.3.2 Brain Region Parcellation: Shen's 268 region atlas [45] was used to parcellate the resting state brain into 268 functionally segregated ROIs using MarsBaR toolbox.

The RsfMRI BOLD time series for each ROI was extracted as the average of all the voxels in that ROI.

2.3.3 Phase-locking matrices and dynamic functional connectivity (DFC): To calculate the instantaneous phase of the BOLD signal, $\phi_k(t)$, we first band-pass filtered the BOLD timeseries corresponding to the brain area k in narrowband of 0.03-0.09 Hz. This frequency band has been mapped to the gray matter and found to capture more relevant information than any other frequency bands in terms of brain function. We computed the instantaneous $\phi_k(t)$ using the Hilbert transform '*H'* which yields the associated analytical signal. The analytical signal represents a narrowband signal, $s(t)$, in time domain as a rotating vector with an instantaneous phase, $\phi_k(t)$, and an instantaneous amplitude, $A(t)$, i.e., $s(t) = A(t).cos\big(\phi(t)\big)$. The phase and the amplitude are given by the argument and the modulus, respectively, of the complex signal, $z(t)$, given by $z(t) = s(t) + i.H[s(t)]$, where i is the imaginary unit and $H[s(t)]$ is the Hilbert transform of $s(t)$.

The synchronization between pairs of brain regions was computed using the difference in instantaneous phases. For each time-point, the instantaneous phase-locking matrix was given as:

$$P_{jk}(t) = e^{i\left(\phi_j(t) - \phi_k(t)\right)} \vee \qquad (1)$$

where $\phi_j(t)$ is the extracted phase of brain area *j* at time *t*. The phase lock matrix describes the states of phase configuration and it has been proposed to contain relevant information for measuring global integration [46] and broadcasting of information [33]. The presence of repeating synchronized networks by calculating the recurrence matrix of phase-locking patterns is the measure of DFC. This measure was previously defined for FC matrices calculated in different time windows [47]. To assess whole brain functional connectivity differences, we averaged all the DFC matrices across time for each group/condition (Figure 1).

2.3.3.1 Integration: We used the phase-locking matrix to compute the level of integration at time *t* based on the procedure presented in [46]. The integration, ϕ, was determined using the length of the largest connected component of the phase-locking matrix $P_{jk}(t)$. More specifically, for a given absolute threshold between 0 and 1 (scanning the whole range), the phase-locking matrix was binarized and its largest

connected component was detected (i.e., the largest sub-group in which any two vertices are connected to each other by paths, and which connects to no additional vertices in the super-graph). The integration, ϕ, was defined as the size of the largest connected component.

2.3.3.2 Segregation: Similar to integration, we extracted the community structure of the phase-locking matrix for each time window *t*. Communities were detected using the Louvain algorithm that performs a subdivision of the matrix into non-overlapping groups of nodes which maximizes the number of within-group edges and minimizes the number of between-group edges [48]. The modularity index, Q, measures the statistics of the community detection. [49].

2.3.3.3 Metastability: To measure the global level of phase synchronization we used the Kuramoto order parameter [37], defined as the average phase of the system of N signals:

$$R(t) = \frac{1}{N} \vee \sum_{k=1}^{N} e^{i\phi_k(t)} \vee \qquad (2)$$

For independent signals, the N phases are uniformly distributed and thus R is nearly zero, whereas $R = 1$ if all phases are equal (full synchronization). In order to promote efficient information processing, the phases of different areas must be synchronized into coherent neural activity. The metastability measure [50] quantifies the temporal variability (of this synchronization) *R(t)* and it is measured by its standard deviation.

2.3.3.4 Intrinsic Ignition: The capability of a given local node to propagate neural activity to other regions was quantified using the intrinsic ignition method [33, 34]. Intrinsic ignition describes the influence of spontaneously occurring events within the network over time. The propagation of neural activity was measured using the global integration, (ϕ), previously described [33], which determines the capacity of the whole network to become interconnected and exchange information. Local events are defined region wise as significantly large fluctuations taking place in the resting-state BOLD signal. To this end, first, the BOLD signals were z-scored (i.e., $Z_i(t)$) and then binarized by imposing a threshold θ (i.e., ± 2 standard deviation above the mean BOLD signal). This resulted in binary time-series per region for which events are indicated with 1 [i.e., $\sigma_i(t) = 1$, if $Z_i(t) > 0$ and $\sigma_i(t) = 0$, otherwise [34]]. Next, for each node

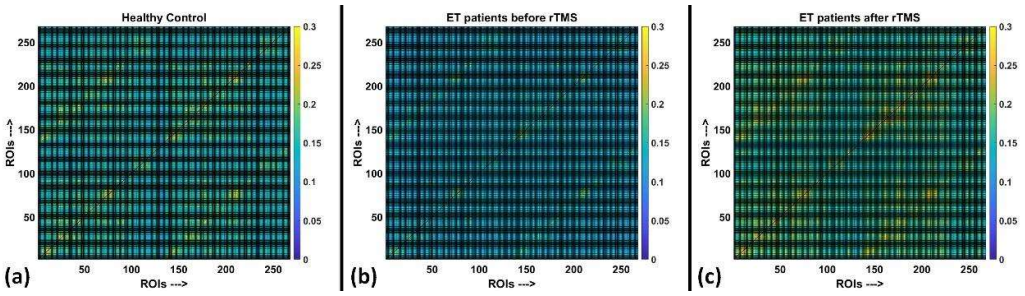
'i', we calculated ϕ in a window of 4 TR after each triggering event (i.e., $\sigma_i(t) = 1$). Finally, the average ϕ over all triggering events was calculated to define the Ignition Driven Mean Integration (IDMI) denoted as "Intrinsic Ignition" [34].

3. Result:

A single session of rTMS was found to increase integration and decrease segregation in patients with ET. Metastability and intrinsic ignition were found to be higher after rTMS at a group level and at individual patient level. Details of these results are as follows:

3.1 Dynamics Functional connectivity (DFC):

The whole brain (i.e., averaged over time and regions) DFC was higher in controls (0.16±0.11) than ET patients (0.06±0.03; p=1.199E-06). After rTMS the patients with ET showed significantly increased mean connectivity (0.23±0.09; p=1.415E-13). The mean connectivity matrices are demonstrated in Figure 1.



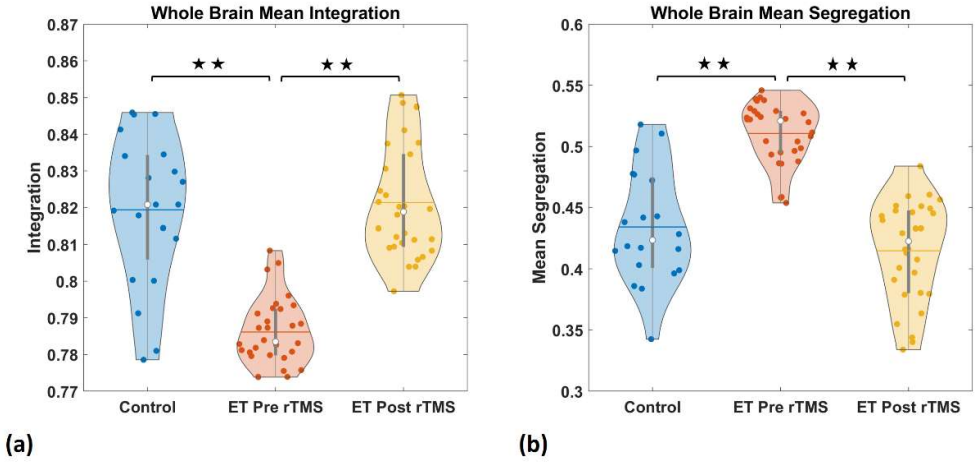
-Figure 1-

Figure 1. Mean dynamic functional connectivity (DFC) matrix of (a) healthy controls (b) ET before rTMS (c) ET after rTMS stimulus. The DFC matrix shows ET having lower functional connectivity as compared to healthy control, which increased after rTMS.

3.2 Whole Brain Integration and Segregation:

The mean value of the integration was significantly lower for patients with ET with respect to controls (controls: 0.82±0.02; ET patients in pre rTMS: 0.79±0.009; p= 4.14E-10); after rTMS the brain integration revealed significant increase (0.82±0.01; p=1.419E-14). On the other hand, the brain segregation showed the opposite tendency

of integration with increased segregation noted in patients at baseline (controls: 0.43±0.04; ET patients in pre rTMS: 0.51±0.02; p=8.84E-10), that decreased after rTMS (0.41±0.04; p=8.65E-15) (Figure 2).

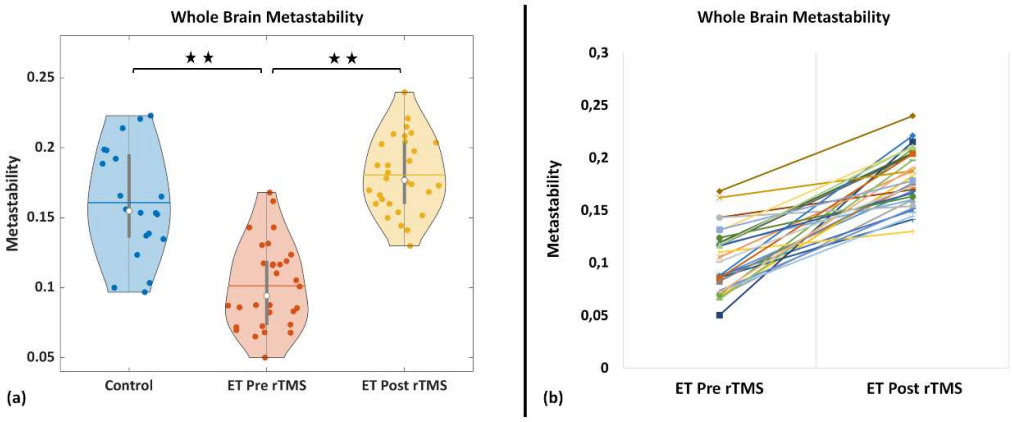


-Figure 2-

Figure 2. Whole brain (a) network integration and (b) segregation. ET has lower network integration and higher segregation as compared to healthy controls. After rTMS, brain network integration increased, and segregation decreased in ET.

3.3 Metastability:

We found that, the mean metastability was lower in ET (0.1±0.03; p=2.25E-07) compared to control (0.16±0.04). After rTMS stimulation the brain metastability significantly increased (0.18±0.03; p=2.31E-14) (Figure 3.a). We also looked for individual subject metastability, and noted that, all subjects had increased metastability after rTMS stimulation (Figure 3.b).

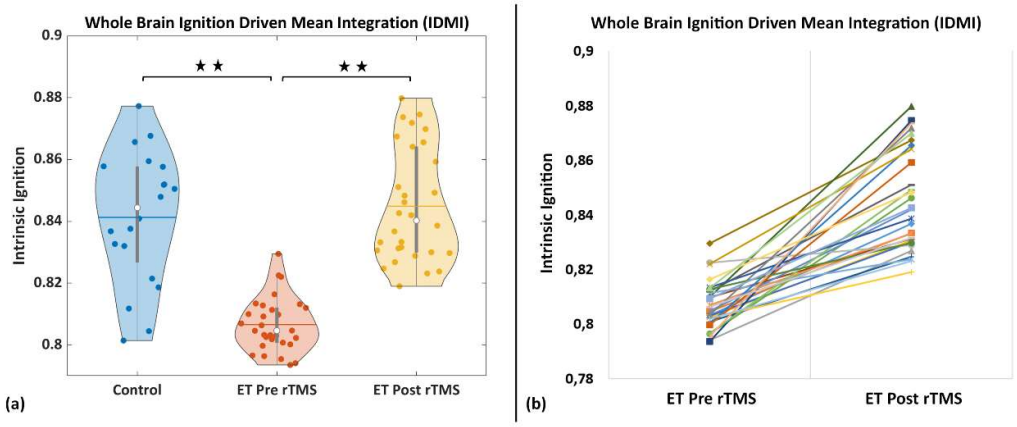


-Figure 3-

Figure 3. Whole brain metastability (a) in violin plot representations for healthy control, ET pre and post rTMS and (b) individual subject whole-brain metastability pre and post rTMS in ET, depicting significant (* FDR p-value <0.001) increase in metastability after rTMS.

3.4 **Intrinsic Ignition:**

We found that the capacity of neural propagation measured by whole brain intrinsic ignition was significantly lower in ET (0.8±0.008; p=2.48E-10) when compared to control (0.84±0.02). After rTMS stimulation, the capacity of neural propagation significantly increased (0.84±0.018; p=7.05E-14) (Figure 4.a). We also analyzed region wise intrinsic ignition and noted, all brain regions have increased intrinsic ignition after rTMS [Supplementary Figure 1]. Further looking at individual subjects, we noted all the subjects having increased whole brain IDMI after rTMS stimulation (Figure 4.b).



-Figure 4-

Figure 4. Whole Brain Ignition Driven Mean Integration (IDMI) (a) in violin plot representations for healthy control, ET pre and post rTMS and (b) individual subject whole-brain IDMI pre and post rTMS in ET, depicting significant (* FDR p-value <0.001) increase in IDMI after rTMS.

4. Discussion:

In this study, we used low-frequency rTMS in patients with ET to understand its mechanism of action, within the framework of brain network integration-segregation, intrinsic ignition, and metastability. In individuals with ET compared to HC at baseline, we saw considerably weaker integration, more segregation, low metastability, and low intrinsic ignition. A single rTMS session was found to reset these metrics by raising global integration, metastability, and intrinsic ignition to levels that were similar to those of healthy controls.

Simulated computational models on metastability reveal small worldness, network interaction and degree of the structural connectivity to have positive predictive value on metastability [51]. Increased pathlength was associated with a decrease in metastability [52]. In the current study, there was reduced segregation and increased global integration after rTMS which is in line with the evidence from computational models and support increased global integration and reduced dynamism between nodes as one of the major determinants for improved metastability. Our prior work in patients with Writer's cramp (WC) had revealed increased clustering coefficient, increased small worldness and reduced pathlength after single session of rTMS [23]. Though a

reduction in pathlength after rTMS, which denote increased network integration was a common denominator in both ET and WC, it needs to be noted that these diseases revealed opposite effects on the network segregation (i.e., clustering coefficient). In WC, brain network segregation increased whereas in ET it decreased. TMS studies have earlier reported differences between patients with ET and dystonic tremor with authors speculating that the thalamo-cortical part of CTC to be playing a prominent role in tremor genesis in patients with ET [53] whereas in patients with dystonic tremor the debate between oscillators within CTC or basal ganglia projections causing tremor is still ongoing [54]. Not discrediting the obvious differences in analyses methods between TMS and DFC we hypothesize that the findings we report could also be due to disease specific alterations in the network morphology. Future studies that are hypothesis driven and focused will be required to answer questions on the disease specific variations in the CTC network after rTMS.

Further exploring the spatio-temporal aspects of brain dynamics, we found that rTMS increased brain metastability and neural propagation capacity as determined by intrinsic ignition. Because one evaluates brain stability and the other the brain's ability to spread neural activation, metastability and intrinsic ignition are complementary assessments of one another. According to a study on diffuse axonal injury, structural disconnection, decreased cognitive flexibility, and information processing were all associated with altered metastability [52]. Decreased metastability and ignition has been reported in unresponsive wakeful state and have been found to increase as patients regain consciousness or reach minimal conscious state [51, 55]. Neural responses to perturbations (i.e., TMS) in patients with unresponsive wakeful states, in contrast to patients in minimally conscious states [56, 57] provides proof of evidence that rTMS increases brain activity and connectivity and supports findings in the current study. Since metastability and intrinsic ignition increased in all subjects, it is possible that the measure may have the ability to evaluate the impact of rTMS at an individual subject level. We did not record changes in behavioral or cognitive scores after rTMS since clinically evident changes after single session of rTMS is less known. However, it seems reasonable to assume that increased metastability and intrinsic ignition measures could be further explored to ascertain its comparability with observed improvement in clinical scores in patients undergoing rTMS therapy.

The study had some limitations. First, the effect of sham stimulation in brain dynamics was not evaluated, and all patients were given real low frequency rTMS intervention. Second, we did not assess the effect of low frequency rTMS stimulation on healthy controls. Third, the described metastability alterations that we have observed are within 10 minutes of single session of rTMS. It will be interesting to consider changes during stimulation and assess how long these alterations will persist to ensure that these changes are not due to anxiety, pain, or fatigue that are associated with rTMS.

5. Conclusion:

Our findings offer substantial evidence that rTMS alters dynamic functional connectivity measures especially brain metastability and intrinsic ignition. However, further research is necessary to make sure that these alterations are sustainable and can quantify the magnitude of changes required for clinically significant improvement.

Acknowledgements:

This work was supported by the Department of Science and Technology - Cognitive Science Research Initiative (DST-CSRI), Government of India [Grant number: SR/CSRI/162/2013]. Mr. Sujas Bhardwaj is currently a Senior Research Fellow under the Wellcome DBT India Alliance Intermediate Fellowship [IA/CPHI/17/1/503348] of Dr. Shantala Hegde (Additional Professor, Music Cognition Lab, NIMHANS, Bengaluru-29, India). We acknowledge contribution of (Late) Dr. Venkateswara Reddy Reddam in the project and preparation of the initial draft of the manuscript.

Author Contribution:

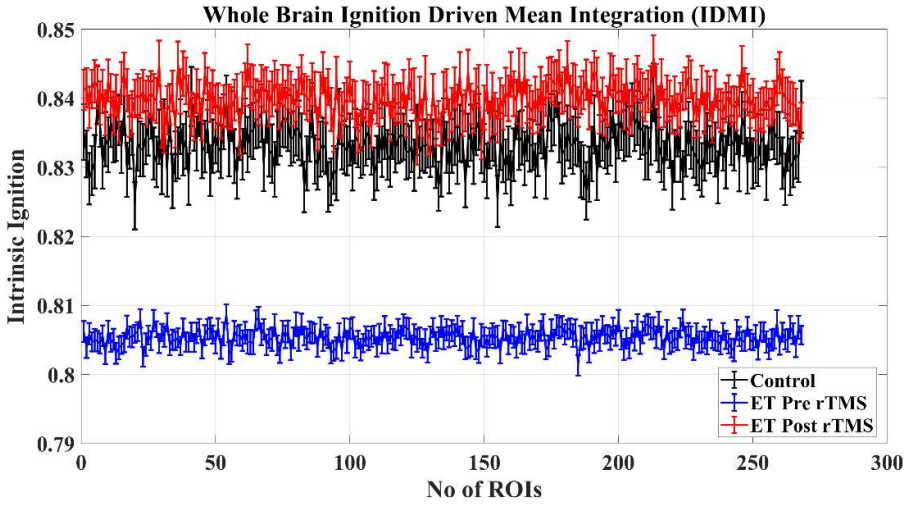
RDB and PKP conceptualized and designed the experiment. PKP, RY, NK, AS, and SP did the clinical assessment of the patients scoring for inclusion criteria. AS, SB and KU provided the rTMS to the subjects. SB, SKK and RDB acquired the MRI data. KK and VT performed neuropsychological assessments. SB, RP, and RDB analyzed the data, and RDB, SB, RP, and PKP interpreted the results. RDB, PKP, JA, and SL supervised the method development. JA, SL, KU, and RK provided a critical review. RDB, SB, and RP wrote the manuscript. All the authors interpreted the results, edited, and approved the manuscript. There is no conflict of interest from any authors in this study.

References:

[1] George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6(14):1853-6.
[2] Holtzheimer PE, 3rd, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depress Anxiety 2010;27(10):960-3.
[3] Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 2008;69(2):222-32.
[4] Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe P, et al. Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder. Neuropsychopharmacology 2014;39(2):488-98.
[5] George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154(12):1752-6.
[6] Grossheinrich N, Rau A, Pogarell O, Hennig-Fast K, Reinl M, Karch S, et al. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. Biol Psychiatry 2009;65(9):778-84.
[7] Arumugham SS, Vs S, Hn M, B V, Ravi M, Sharma E, et al. Augmentation Effect of Low-Frequency Repetitive Transcranial Magnetic Stimulation Over Presupplementary Motor Area in Obsessive-Compulsive Disorder: A Randomized Controlled Trial. J ECT 2018;34(4):253-7.
[8] Hawken ER, Dilkov D, Kaludiev E, Simek S, Zhang F, Milev R. Transcranial Magnetic Stimulation of the Supplementary Motor Area in the Treatment of Obsessive-Compulsive Disorder: A Multi-Site Study. Int J Mol Sci 2016;17(3):420.
[9] Kumar S, Singh S, Chadda RK, Verma R, Kumar N. The Effect of Low-Frequency Repetitive Transcranial Magnetic Stimulation at Orbitofrontal Cortex in the Treatment of Patients With Medication-Refractory Obsessive-Compulsive Disorder: A Retrospective Open Study. J ECT 2018;34(2):e16-e9.
[10] Ma X, Huang Y, Liao L, Jin Y. A randomized double-blinded sham-controlled trial of alpha electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. Chin Med J (Engl) 2014;127(4):601-6.
[11] Isserles M, Shalev AY, Roth Y, Peri T, Kutz I, Zlotnick E, et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder--a pilot study. Brain Stimul 2013;6(3):377-83.
[12] Nam DH, Pae CU, Chae JH. Low-frequency, Repetitive Transcranial Magnetic Stimulation for the Treatment of Patients with Posttraumatic Stress Disorder: a Double-blind, Sham-controlled Study. Clin Psychopharmacol Neurosci 2013;11(2):96-102.
[13] Watts BV, Landon B, Groft A, Young-Xu Y. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Brain Stimul 2012;5(1):38-43.
[14] Pinto AD, Lang AE, Chen R. The cerebellothalamocortical pathway in essential tremor. Neurology 2003;60(12):1985-7.
[15] Frey J, Hess CW, Kugler L, Wajid M, Wagle Shukla A. Transcranial Magnetic Stimulation in Tremor Syndromes: Pathophysiologic Insights and Therapeutic Role. Front Neurol 2021;12:700026.
[16] Bharath RD, Biswal BB, Bhaskar MV, Gohel S, Jhunjhunwala K, Panda R, et al. Repetitive transcranial magnetic stimulation induced modulations of resting state motor connectivity in writer's cramp. Eur J Neurol 2015;22(5):796-805, e53-4.
[17] Brabenec L, Klobusiakova P, Barton M, Mekyska J, Galaz Z, Zvoncak V, et al. Non-invasive stimulation of the auditory feedback area for improved articulation in Parkinson's disease. Parkinsonism Relat Disord 2019;61:187-92.
[18] Xue SW, Guo Y, Peng W, Zhang J, Chang D, Zang YF, et al. Increased Low-Frequency Resting-State Brain Activity by High-Frequency Repetitive TMS on the Left Dorsolateral Prefrontal Cortex. Front Psychol 2017;8:2266.

[19] Zhang H, Sollmann N, Castrillon G, Kurcyus K, Meyer B, Zimmer C, et al. Intranetwork and Internetwork Effects of Navigated Transcranial Magnetic Stimulation Using Low- and High-Frequency Pulse Application to the Dorsolateral Prefrontal Cortex: A Combined rTMS-fMRI Approach. J Clin Neurophysiol 2020;37(2):131-9.
[20] Ji GJ, Yu F, Liao W, Wang K. Dynamic aftereffects in supplementary motor network following inhibitory transcranial magnetic stimulation protocols. Neuroimage 2017;149:285-94.
[21] Schluter RS, Jansen JM, van Holst RJ, van den Brink W, Goudriaan AE. Differential Effects of Left and Right Prefrontal High-Frequency Repetitive Transcranial Magnetic Stimulation on Resting-State Functional Magnetic Resonance Imaging in Healthy Individuals. Brain Connect 2018;8(2):60-7.
[22] Watanabe T, Hanajima R, Shirota Y, Ohminami S, Tsutsumi R, Terao Y, et al. Bidirectional effects on interhemispheric resting-state functional connectivity induced by excitatory and inhibitory repetitive transcranial magnetic stimulation. Hum Brain Mapp 2014;35(5):1896-905.
[23] Bharath RD, Panda R, Reddam VR, Bhaskar MV, Gohel S, Bhardwaj S, et al. A Single Session of rTMS Enhances Small-Worldness in Writer's Cramp: Evidence from Simultaneous EEG-fMRI Multi-Modal Brain Graph. Front Hum Neurosci 2017;11:443.
[24] Tik M, Hoffmann A, Sladky R, Tomova L, Hummer A, Navarro de Lara L, et al. Towards understanding rTMS mechanism of action: Stimulation of the DLPFC causes network-specific increase in functional connectivity. Neuroimage 2017;162:289-96.
[25] Vink JJT, Mandija S, Petrov PI, van den Berg CAT, Sommer IEC, Neggers SFW. A novel concurrent TMS-fMRI method to reveal propagation patterns of prefrontal magnetic brain stimulation. Hum Brain Mapp 2018;39(11):4580-92.
[26] Thut G, Miniussi C. New insights into rhythmic brain activity from TMS-EEG studies. Trends Cogn Sci 2009;13(4):182-9.
[27] Jung J, Bungert A, Bowtell R, Jackson SR. Vertex Stimulation as a Control Site for Transcranial Magnetic Stimulation: A Concurrent TMS/fMRI Study. Brain Stimul 2016;9(1):58-64.
[28] Song D, Chang D, Zhang J, Peng W, Shang Y, Gao X, et al. Reduced brain entropy by repetitive transcranial magnetic stimulation on the left dorsolateral prefrontal cortex in healthy young adults. Brain Imaging Behav 2019;13(2):421-9.
[29] Castrillon G, Sollmann N, Kurcyus K, Razi A, Krieg SM, Riedl V. The physiological effects of noninvasive brain stimulation fundamentally differ across the human cortex. Sci Adv 2020;6(5):eaay2739.
[30] Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. Neuron 2011;72(4):665-78.
[31] Kelso JA. Multistability and metastability: understanding dynamic coordination in the brain. Philos Trans R Soc Lond B Biol Sci 2012;367(1591):906-18.
[32] Kelso JA. Instabilities and phase transitions in human brain and behavior. Front Hum Neurosci 2010;4:23.
[33] Deco G, Kringelbach ML. Hierarchy of Information Processing in the Brain: A Novel 'Intrinsic Ignition' Framework. Neuron 2017;94(5):961-8.
[34] Deco G, Tagliazucchi E, Laufs H, Sanjuan A, Kringelbach ML. Novel Intrinsic Ignition Method Measuring Local-Global Integration Characterizes Wakefulness and Deep Sleep. eNeuro 2017;4(5).
[35] Bhowmik D, Shanahan M. Metastability and inter-band frequency modulation in networks of oscillating spiking neuron populations. PLoS One 2013;8(4):e62234.
[36] Chialvo DR. Emergent complex neural dynamics. Nature Physics 2010;6:744–50.
[37] Deco G, Kringelbach ML. Metastability and Coherence: Extending the Communication through Coherence Hypothesis Using A Whole-Brain Computational Perspective. Trends Neurosci 2016;39(3):125-35.
[38] Friston KJ. Transients, metastability, and neuronal dynamics. Neuroimage 1997;5(2):164-71.
[39] Hellyer PJ, Shanahan M, Scott G, Wise RJ, Sharp DJ, Leech R. The control of global brain dynamics: opposing actions of frontoparietal control and default mode networks on attention. J Neurosci 2014;34(2):451-61.
[40] Tognoli E, Kelso JA. The metastable brain. Neuron 2014;81(1):35-48.
[41] Werner G. Metastability, criticality and phase transitions in brain and its models. Biosystems 2007;90(2):496-508.
[42] Beynel L, Powers JP, Appelbaum LG. Effects of repetitive transcranial magnetic stimulation on resting-state connectivity: A systematic review. Neuroimage 2020;211:116596.

[43] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord 2018;33(1):75-87.
[44] Louis ED, Ford B, Lee H, Andrews H, Cameron G. Diagnostic criteria for essential tremor: a population perspective. Arch Neurol 1998;55(6):823-8.
[45] Shen X, Tokoglu F, Papademetris X, Constable RT. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. Neuroimage 2013;82:403-15.
[46] Deco G, Tononi G, Boly M, Kringelbach ML. Rethinking segregation and integration: contributions of whole-brain modelling. Nat Rev Neurosci 2015;16(7):430-9.
[47] Glerean E, Salmi J, Lahnakoski JM, Jaaskelainen IP, Sams M. Functional magnetic resonance imaging phase synchronization as a measure of dynamic functional connectivity. Brain Connect 2012;2(2):91-101.
[48] Mohr H, Wolfensteller U, Betzel RF, Misic B, Sporns O, Richiardi J, et al. Integration and segregation of large-scale brain networks during short-term task automatization. Nat Commun 2016;7:13217.
[49] Sporns O. Network attributes for segregation and integration in the human brain. Curr Opin Neurobiol 2013;23(2):162-71.
[50] Deco G, Kringelbach ML, Jirsa VK, Ritter P. The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. Sci Rep 2017;7(1):3095.
[51] Lopez-Gonzalez A, Panda R, Ponce-Alvarez A, Zamora-Lopez G, Escrichs A, Martial C, et al. Loss of consciousness reduces the stability of brain hubs and the heterogeneity of brain dynamics. Commun Biol 2021;4(1):1037.
[52] Hellyer PJ, Scott G, Shanahan M, Sharp DJ, Leech R. Cognitive Flexibility through Metastable Neural Dynamics Is Disrupted by Damage to the Structural Connectome. J Neurosci 2015;35(24):9050-63.
[53] Lu MK, Chiou SM, Ziemann U, Huang HC, Yang YW, Tsai CH. Resetting tremor by single and paired transcranial magnetic stimulation in Parkinson's disease and essential tremor. Clin Neurophysiol 2015;126(12):2330-6.
[54] Madelein van der Stouwe AM, Nieuwhof F, Helmich RC. Tremor pathophysiology: lessons from neuroimaging. Curr Opin Neurol 2020;33(4):474-81.
[55] Panda R, Lopez-Gonzalez A, Gilson M, Gosseries O, Thibaut A, Frasso G, et al. Posterior integration and thalamo-frontotemporal broadcasting are impaired in disorders of consciousness. https://wwwbiorxivorg/ 2021.
[56] Thibaut A, Panda R, Annen J, Sanz LRD, Naccache L, Martial C, et al. Preservation of Brain Activity in Unresponsive Patients Identifies MCS Star. Ann Neurol 2021;90(1):89-100.
[57] Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, et al. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med 2013;5(198):198ra05.



Supplementary Figure 1. Region-wise [45] plot of Ignition Driven Mean Integration (IDMI) for healthy controls, ET pre and post rTMS.

Supplementary Table 1: Clinical and cortical excitability measures in subjects with essential tremor

NAME	Age	Gender	AAO	DD	RMT	AMT	CMCT [ms]	CSP
Subject 001	47	M	38	9	36	30	7.57	98.6
Subject 002	24	M	20	4	35	31	8.6	64.8
Subject 003	27	M	19	8	42	39	7.2	66.4
Subject 004	25	M	21	4	44	41	9.5	52.8
Subject 005	36	M	26	10	39	32	7.8	59.3
Subject 006	22	M	7	15	38	31	8.1	66.4
Subject 007	44	F	43	1	47	36	8.95	67.2
Subject 008	32	M	17	15	40	34	8.2	48.4
Subject 009	32	F	31	1	38	34	6.8	62.6
Subject 010	41	F	38	3	39	29	6.9	67.9
Subject 011	50	M	36	14	34	30	4.7	52.8
Subject 012	42	M	37	5	30	28	5.8	58.4
Subject 013	45	F	44.5	0.5	38	29	6.6	55.3
Subject 014	35	M	22	13	39	31	5.9	59.1
Subject 015	41	M	34	7	32	26	7.4	42.8
Subject 016	28	M	13	15	34	30	8.45	46.4
Subject 017	47	M	46	1	70	62	15.5	46.6
Subject 018	23	M	16	7	24	22	7.9	37.6
Subject 019	32	M	28	4	36	32	7.5	78.4
Subject 020	25	M	24	1	32	26	8.24	48.4
Subject 021	35	M	21	14	40	26	6.6	117.2
Subject 022	55	M	54	1	38	36	5.4	48
Subject 023	54	M	53	1	40	38	6.8	86.2
Subject 024	20	F	14	6	28	25	7.4	64
Subject 025	46	M	41	5	30	22	9.1	52.2
Subject 026	33	M	31	2	38	32	8.3	56.7
Subject 027	26	F	22.5	3.5	38	34	8.6	46.8
Subject 028	49	M	44	5	42	32	6.8	91.5
Subject 029	54	M	53	1	44	38	4.4	54
Subject 030	51	M	49	2	42	34	5.4	78.6

AAO: age at onset; DD: Disease duration; RMT: Resting Motor Threshold, AMT: Active Motor Threshold, CMCT: Central Motor Conduction Time; CSP: Contralateral Silent Period.