



Reduced brain entropy by repetitive transcranial magnetic stimulation on the left dorsolateral prefrontal cortex in healthy young adults

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Abstract

Entropy indicates system irregularity and the capacity for information processing. Recent research has identified interesting voxel-wise entropy distribution patterns in normal brain and its changes due to aging and brain disorders. A question of great scientific and clinical importance is whether brain entropy (BEN) can be modulated using non-invasive neuromodulations. The purpose of this study was to address this open question using high-frequency repetitive transcranial magnetic stimulation (rTMS). BEN was calculated from resting state fMRI at each voxel acquired before and after applying 20 Hz rTMS or SHAM (control) stimulation. As compared to SHAM, 20 Hz rTMS reduced BEN in medial orbito-frontal cortex and subgenial anterior cingulate cortex (MOFC/sgACC), suggesting a reduced information processing therein, probably as a result of the enhanced top-down regulation by the left DLPFC rTMS. No significant changes were observed to the functional connectivity (FC) between the left DLPFC (the target site) to the rest of the brain, suggesting that rTMS may not affect FC though it might use FC to transfer its effects or the ad hoc information. Our data proved that rTMS can modulate BEN and BEN can be used to monitor rTMS effects.

Keywords rTMS · Brain entropy · Resting state fMRI

Introduction

Human brain is one of if not the most complex system known to us (Baar 2010; Singer 2009). Its defining and elusive complexity has long been postulated as an essential property for executing highly complicated cognitive functions such as memory and language, for adapting to internal neuronal interactions such as inhibition, or for adapting to the constantly changing environment (Baar 2010; Singer 2009). Theoretical models and empirical data have shown that normal brain activity reaches a critical point between a totally coherent regime (such as coma or slow wave sleep) and a

more chaotic regime (Deco and Jirsa 2012; Friston et al. 1992; Friston et al. 1995; Kiebel et al. 2008; Rubinov et al. 2011; Tononi et al. 1994) to maximize its complexity so as to maximize its capacity for interactions. Such critical point and the corresponding complexity, however, may be altered by aging (Lipsitz 2011; Sosnoff et al. 2007; Yang et al. 2013) or neuropathological conditions (Bruna et al. 2012; Costa et al. 2002, 2005; Fernandez et al. 2010; Gomez et al. 2011; Rosso et al. 2002; Yang et al. 2015). Characterizing brain complexity may then provide a systematic insight on functional brain capacity for function and adaptation/interaction and its alterations during disease conditions, which may subsequently provide a sensitive way for monitoring the effects of treatment or medications.

Complexity is widely characterized by entropy which quantifies the irregularity or incoherence of a dynamic system (Sandler 2006). We have recently proposed an fMRI-based method (Wang et al. 2014) to map the whole brain temporal complexity using a nonparametric entropy metric, the Sample Entropy (Lake et al. 2002; Richman and Moorman 2000). This measure is based upon the entropy of measured haemodynamic states that considers dependency over time using temporal embedding. In other words, this use of entropy

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reflects the statistical dependencies or order implicit in itinerant dynamics, expressed over extended periods of time. Using the BEN mapping tool, we found that normal brain presents structurally and functionally meaningful BEN patterns at rest which was reproducible across different time (Wang et al. 2014). We then observed that BEN can be boosted up by caffeine intake (Da Chang et al. 2018), it also showed disease-related alterations in several brain disorders including multiple sclerosis (Zhou et al. 2016), chronic cigarette smoking (Li et al. 2016a), and cocaine addiction (Ze Wang et al. 2016). Other group also reported BEN alterations in different brain states including normal aging (Yang et al. 2013; Yao et al. 2013), Schizophrenia (Sokunbi et al. 2014a), and attention deficit hyperactivity disorder (ADHD) (Sokunbi et al. 2014b). Together, these studies evidenced the potential of assessing BEN as a biomarker for various brain disorders. It is then of great scientific and clinical research interest to see whether BEN can be altered by any medication, treatment, or neuromodulation. The current study represents an initial endeavor toward those important research topics. Our goal was to examine whether regional BEN could be altered by non-invasive neuromodulations through transcranial magnetic stimulation (TMS) (Barker et al. 1985).

TMS is a noninvasive neuro-modulation technique that has been widely used in neuroscience research (Bolognini and Ro 2010; Pascual-Leone et al. 2000; Walsh and Cowey 2000) and treatment research for various neuropsychological or neuropsychiatric disorders (Fregni and Pascual-Leone 2007; Lan et al. 2016; Machado et al. 2013; Rossini and Rossi 2007; Slotema et al. 2010; Trojak et al. 2015). TMS effects rely on a changing magnetic field induced by fast and frequently charging and discharging a capacitor (Hallett 2000; Hoogendam et al. 2010). The magnetic field can penetrate the intact scalp losslessly and induce weak electrical currents in the superficial cortex, which interacts with the ongoing neuronal activity, leading to macroscopic deactivations or excitations of the affected brain regions (Allen et al. 2007). These neuronal interactions can be sustained for a long time by repetitive application of TMS (rTMS) (Hallett 2007; Hoogendam et al. 2010). Because of that, rTMS is now widely used in treatment studies for various neuro-psychiatric or neuro-psychological disorders (Lan et al. 2016; B. Trojak et al. 2015). In the literature, high-frequency (>1 Hz) rTMS is often cited for its excitatory effects on neuronal activity (Wobrock et al. 2015). It even becomes the first US Food and Drug Administration approved protocol for treating the medically resistant depression (George et al. 2010; O'Reardon et al. 2007) (FDA approval K061053). We chose the left dorsal lateral frontal cortex (DLPFC) as the target site for applying rTMS or SHAM because it is the most widely used site in many basic and clinical rTMS research due to its pivotal role in many high-order brain functions such as attention (Knight et al. 1995; Kondo et al. 2004), working memory

(Balconi 2013; Curtis and D'Esposito 2003; Mars and Grol 2007; Mull and Seyal 2001), cognition control (MacDonald et al. 2000), and decision-making (Glenn et al. 2009; Heekeren et al. 2004; Hutcherson et al. 2012). We expected to see that brain activity in the target site (DLPFC) and its projected areas would become more coherent after receiving rTMS. Such coherence increase would manifest as a reduction of BEN. In order to avoid the effects of the placebo and other artifact (acoustic artifact, scalp muscle stimulation, daily experimenter contact) (Lisanby et al. 2001), our experiment used sham-controlled design, which the most common sham conditions angle the coil 90° off the head so that the magnetic field stimulates scalp muscles and produces an acoustic artifact, but presumably does not induce current in the cortex.

Methods

Participants

Forty-eight healthy participants (age: 22.92 ± 2.97 years, 21 males, 27 females) participated in the experiment. All participants are right-handed and reported no history of neurological or psychiatric disorders. All the participants were randomly divided into the SHAM ($n = 18$, aged 23.44 ± 3.40 years, 6 males) and rTMS ($n = 30$, aged 22.60 ± 2.69 years, 15 males) group. SHAM here means having the subjects expose to the same experiment environment as in rTMS but without stimulating the brain (see next paragraph for more details). For each group, participants received two sessions of MRI scans in two separate days with 48 h apart using the same imaging protocols: The baseline scan (without SHAM or rTMS) and the post-rTMS or SHAM scan. The post-stimulation scan was performed right after rTMS (post-rTMS) or SHAM stimulation (post-SHAM) (within 15 min due to the pre-scan preparations) to ensure that the stimulation effects are measured (Siebner et al. 2009). The 48 h' interval between the two sessions was chosen to avoid any residual rTMS. All study procedures adhered to the Declaration of Helsinki were approved by local IRB and all participants signed written consent forms before participating in any experiment.

rTMS

rTMS was performed using a Magstim Rapid stimulator (Magstim Ltd, Whitland, UK) with a figure-of-eight coil. ABrainsight frameless stereotaxy system was used for neuronavigation (Magstim Ltd, Whitland, UK). Each subject's structural MRI was skull-stripped and registered into the Montreal Neurological Institute (MNI) standard brain. The stimulation target site: left DLPFC was set to be the location of (-40, 26, 37) (Guse et al. 2010) in the MNI space and projected into the individual subject's preprocessed 3D

structural MRI. The target site on the brain was mapped to the subject's scalp by interactively matching the focus of TMS coil to the target in the 3D brain space reconstructed in the neuronavigation system.

rTMS was applied following the safety guidance provided by the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulator (Wassermann 1998). rTMS was administered in 12 successive pulse blocks interleaved with 28 s quiet time. Each block consisted of 50 pulses with 20 pulses per second (20 Hz) for 2.5 s. The magnitude of pulse was set to be 90% of the resting motor threshold. The same pulse train was used for SHAM stimulation except that the coil was reoriented to be orthogonal to the direction of rTMS (orthogonal to the skull), which the degree of angulation from the plane tangential to the scalp is typically 90°.

MRI data acquisition

MR imaging was performed in a GE Discovery MR 750 3Tesla scanner (General Electric, Waukesha, WI, USA) at the Center for Cognition and Brain Disorders at Hangzhou Normal University, China. During the scan, a comfortable and tight cushion was placed to immobilize the head and reduce motion. The participants were instructed to relax and remain still with their eyes open, not to fall asleep, and not to think about anything in particular. The screen presented a black fixation point '+' in the center of the gray background. All participants were monitored through the video camera in the scanner room and nobody was found to fall asleep during the scan, which was also confirmed by interview after-scan interview.

High-resolution T1-weighted structural MRI was acquired with a 3D spoiled gradient echo sequence (3D SPGR) with repetition time/echo time (TR/TE) = 8.1/3.39 msec, flip angle = 7°, field of view = 256 × 256 mm, matrix = 256 × 256, 1.0 mm³ isotropic voxels, 176 slices without interslice gap). Resting fMRI was acquired with a T2*-weighted gradient-echo EPI pulse sequence with the following parameters: TR/TE = 2000/30 msec, flip angle = 90°, field of view = 220 × 220 mm², matrix = 64 × 64, 3.4 mm³ isotropic spatial resolution, and 37 interleaved slices. 180 images were acquired in 6 mins.

MRI image preprocessing

MR image preprocessing was performed using Statistical Parametric Mapping (SPM12, WELLCOME TRUST CENTRE FOR NEUROIMAGING, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Structural MRI was registered into the Montreal Neurological Institute (MNI) standard brain space using SPM12. Gray matter, white matter (WM), and cerebrospinal fluid (CSF) segmentation maps were generated during the same normalization process.

The following steps were used for processing rsfMRI images. 1) The first 6 volumes were discarded from each

subject's resting-state fMRI data to allow image intensity to reach steady state; 2) The remaining images were corrected for slice timing acquisition difference using the middle slice as the reference and then corrected for head motions using the first image volume as the reference. All subjects included in the following analyses had no more than 2 mm translational motions and no more than 2 degree of angular motions; 3) rsfMRI images were spatially registered with the high definition structural MRI. WM and CSF segmentation maps were back-registered into the rsfMRI image space and resampled to have the same image resolution to be used as masks for extracting the mean WM and CSF signals; 4) temporal nuisance correction was performed via simple regression by including head motion time courses, WM signal, and cerebrospinal fluid (CSF) signal as nuisance; Global signal regression was not used (Saad et al. 2012). 5) spatial smoothing was done with an isotropic Gaussian kernel with a full-width-at-half-maximum (FWHM) of 6 mm³; 6) rsfMRI images were band-pass filtered (0.01–0.08 Hz) to eliminate high-frequency noise and low-frequency drift; 7) rsfMRI images were warped into the MNI space using the spatial transform estimated from the structural MRI as mentioned above, and resampled with a resolution of 3 × 3 × 3 mm³.

BEN mapping calculation

BEN mapping was performed using the Brain Entropy mapping toolbox (Wang et al. 2014). BEN was calculated from the preprocessed rsfMRI at each voxel using Sample Entropy (SampEn) (Lake et al. 2002). SampEn is an approximate entropy formula determined from the temporal coherence of a time series. It is calculated as the "logarithmic likelihood" that a small section (within a window of a length 'm') of the data "matches" with other sections will still "match" the others if the section window length increases by 1. "match" is defined by a threshold < r times standard deviation of the entire time series. In this study, the window length was set to 3 and the cut off threshold was set to 0.6 (Wang et al. 2014). More details of BEN calculation can be found in the original BENTbx paper (Wang et al. 2014). The collection of all voxels' entropy values formed the BEN map, which was smoothed with an isotropic Gaussian kernel (FWHM = 6 mm³).

Resting-state functional connectivity (FC)

We also examined the rTMS effects on functional connectivity of the DLPFC to the rest of the brain. A sphere with a radius of 6 mm (Bowman et al. 2009; Guo et al. 2015; Markett et al. 2014) was defined in the DLPFC (−40,26,37) using Data Processing Assistant for Resting-State fMRI (Yan and Zang 2010) (DPARSF, www.restfmri.net) as the seed. The mean rsfMRI time course was extracted from the seed and correlated to all voxels in the rest of the brain. The

correlation coefficient was measured as the amplitude of FC. Each subject's FC map was converted to a z map using Fisher's transformation to improve the normality before performing group level analysis.

Statistical analysis

Voxel-wise paired-t test was performed to assess the BEN alterations due to rTMS or SHAM separately. The individual post-pre rTMS BEN difference was then compared with the individual post-pre SHAM BEN difference using two-sample t-test. All these massive univariate statistical analyses were performed using SPM12. Significance level was defined at the voxel level by $p < 0.001$. To correct for multiple comparisons, Monte Carlo simulations were performed 1000 times using the AlphaSim program in Analysis of Functional NeuroImages (AFNI), and the cluster size surviving $\alpha < 0.05$ was 45. Similar analyses were performed for the left DLPFC FC. The BEN comparison suprathreshold cluster was used as a seed and the above FC analysis was performed to further delineate the possible mechanism of the potential rTMS-induced BEN alterations.

Results

Fig. 1 shows the changes of BEN after rTMS or SHAM stimulation. 20 Hz rTMS reduced BEN in medial orbito-frontal cortex (MOFC)/subgenial anterior cingulate cortex (sgACC) (Fig. 1a). By contrast, SHAM didn't produce any BEN alterations (Fig. 1b). A direct comparison between the rTMS induced BEN changes (Fig. 1a) and that by SHAM (Fig. 1b) (equivalent to the stimulation versus time interaction effects in a 2×2 Analysis of Variance model with 2 factors: stimulation (rTMS or SHAM) and time (pre or post-stimulation)) revealed a spatially more extended BEN reduction pattern in mOFC/sgACC (Fig. 1c).

No significant changes to left DLPFC-FC and sgACC-FC were observed after receiving 20 Hz rTMS or SHAM stimulation. No interactions of rTMS and time on left DLPFC-FC or sgACC-FC were observed either.

Discussion

This study provides the first evidence of rTMS-induced BEN changes in the resting brain. After applying 20 Hz rTMS on left DLPFC in young adults' brain, we observed decreased BEN in MOFC/sgACC but no BEN changes in the stimulation target (left DLPFC) and no significant changes to the FC between the stimulation target on left DLPFC and any other place in the brain.

Reduced BEN means reduced brain activity irregularity and information processing capability. While such a reduction may cause the brain to be less flexible for handling various incoming and outgoing information, it can be beneficial to brain function in terms of concentrating more on a certain range of information and less vulnerable to random or incidental distractions especial when such interference is problematic. The high-frequency rTMS affected region: MOFC/sgACC is known to be implicated in many psychiatric diseases such as schizophrenia, depression, and drug addiction etc. MOFC/sgACC plays a pivotal role in many fundamental brain functions, such as reward processing (Rolls 2000), mood regulation (Rempel-Clower 2007; Rule et al. 2002), impulse control (Elliott, R., and Deakin 2005; Knight et al. 1995), and decision making (Fellows 2007; Rushworth et al. 2007) etc (Etkin et al. 2011; J.-M. Fuster 2009; Miller 2000; Posner et al. 2007; Rangel et al. 2008; Spreng et al. 2009), which are often heavily impaired by psychiatric diseases. Interestingly, beneficial effects of high frequency rTMS on left DLPFC have been repeatedly reported in the literature (Balconi and Canavesio 2014; Balconi and Ferrari 2012; Bermudes et al. 2017; George et al. 2010; Hwang et al. 2010; Lam et al. 2008; Machado et al. 2013; O'Reardon et al. 2007; Osoegawa et al. 2018; Varghese et al. 2018), suggesting a dysfunction recovery to regions including

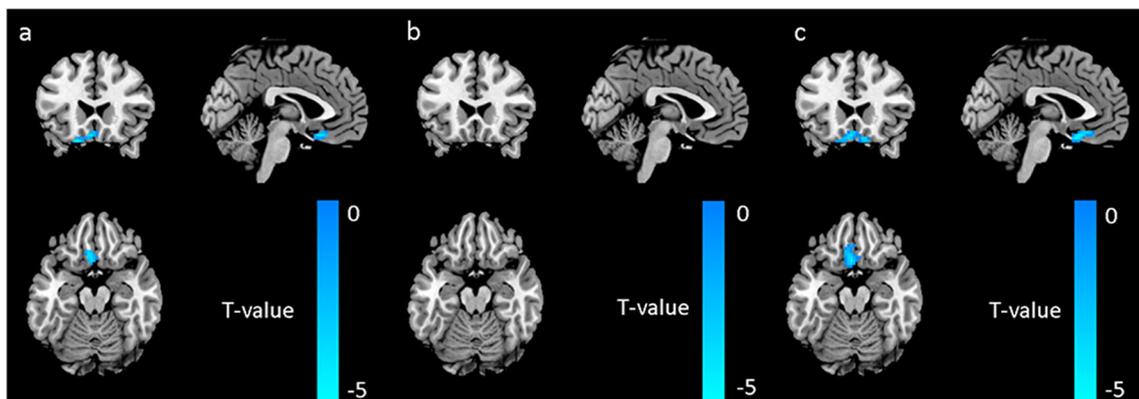


Fig. 1 BEN changes after receiving a) 20 Hz rTMS, b) SHAM stimulations, c) the difference between a and b (the interaction of

stimulation vs time). Cool color means BEN reduction (The figure was created using MRICroN, <https://www.nitrc.org/projects/mricron>)

MOFC/sgACC. In line with those clinical studies, our findings of high-frequency rTMS-induced MOFC/sgACC BEN reduction might implicate a possible mechanism of those widely cited beneficial effects of left DLPFC high-frequency rTMS, i.e., through a reduction of information processing in MOFC/sgACC. Partial support to this postulation comes from 3 entropy studies (Akar et al. 2015; Méndez et al. 2012; P. S. Ho et al. 2017) in depression which found increased entropy in depressive patients and one paper showed Lempel-Ziv complexity (which is similar to entropy) values decreased after effective treatment in young patients.

High frequency rTMS on left DLPFC is widely cited for its excitatory effects (Balconi and Canavesio 2014; Balconi and Ferrari 2012; Hwang et al. 2010). Then why the excitatory rTMS caused inhibitory effects (BEN reduction) in remote places? This seemingly dilemma may be explained by two reasons. First, high frequency DLPFC rTMS enhances the brain's inhibition control, a major function performed by DLPFC (MacDonald et al. 2000). Increased inhibition control could then pose stronger regulations to subcortical brain activity through the top-down regulations (Knight et al. 1995; Kondo et al. 2004) and subsequently brings the irregularity down. These top-down regulation can be through the many efferent or afferent projections of DLPFC from or to MOFC/sgACC (Fuster 2009; McRae et al. 2012; Ochsner et al. 2009; Rolls 2004). Second, the inhibitory effects may be induced by the negative FC between DLPFC and sgACC (Fox et al. 2012), which was shown to be related to the efficacy of rTMS for treating depression (Fox et al. 2012). The rTMS target site in our study was on (−40, 26, 37) in the MNI space (Guse et al. 2010), close to the four different DLPFC spots with high rTMS treatment efficacy and with FC to MOFC/sgACC as evaluated in (Fox et al. 2012). The inverse coupling between MOFC/sgACC and DLPFC may convert the excitatory effects on DLPFC into inhibitory effects on MOFC/sgACC.

We didn't observe significant changes to DLPFC FC. While modulating brain activity with period TMS pulses may increase the coherence between the affected regions, one reason for not observing the coherence increase is that rTMS works by inserting information into the brain (Pasley et al. 2009; Reithler et al. 2011; Romei et al. 2016; Silvanto et al. 2008) which does not necessarily affect the information pathway—the FC here, especially when our data were acquired several minutes after rTMS and the information inserted by rTMS on DLPFC might have been spread into remote regions including MOFC/sgACC. Nevertheless, it is still possible that the beneficial high frequency rTMS will recover FC if it is impaired in diseased condition such as addiction (Gu et al. 2010; Li et al. 2016b).

No significant BEN changes were observed in DLPFC. While we can still see a trend of BEN reduction when more liberal threshold was used, the “no-show” of significant BEN effects of rTMS on the target site may be caused by the large

cross-subject variability as we demonstrated in another two separate studies based on two other brain activity measures (Jun Xie et al. 2018; Xue et al. 2017).

Several limitations must be noted. First, we didn't have behavior data to directly support our postulations about the BEN reduction findings. Second, sample size in control group (SHAM) was smaller than that of rTMS subjects. While having more controls may better reveal the rTMS-induced BEN patterns, additional analysis based on the same number of SHAM and rTMS subjects found similar results to what reported in this paper, meaning that the findings reported were not biased by the sample size in each group. Third, we didn't assess effects of different parameters of rTMS on resting BEN. Several studies have shown that rTMS with different parameters such as intensity and target site can have different effects (Lage et al. 2016; Rossi et al. 2009; Wagner et al. 2009). rTMS is also known to have large inter-subject variability (Maeda et al. 2000; Nettekoven et al. 2015; Ziemann and Siebner 2015). Both may explain why we only observed significant BEN alterations in MOFC/sgACC. For the simplicity of experiment operations, the rTMS target was set to be the same spot in the common brain space, but human brain is known to have large structural and functional variability, meaning that a personalized target site selection may achieve better rTMS effects (Fox et al. 2012), which may also explain the “no-change” finding in the target site. Entropy may empirically present positive correlation to variability, another metric of brain activity that has been attracted increasing attention (D. D. Garrett et al. 2010; Douglas D. Garrett et al. 2011; D. D. Garrett et al. 2013; Li et al. 2016c; Zhang et al. 2016), but entropy is defined on the distribution function of signal rather than merely on the second order moment.

In summary, we provided data showing the hypothetical BEN alterations due to the periodic high-frequency rTMS on left DLPFC. The reduced BEN in MOFC/sgACC may underlie the effectiveness of left DLPFC high-frequency rTMS on various psychiatric disorders.

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Compliance with ethical standards

Conflict of interest All authors declared no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed written consents were obtained from all individual participants included in the study.

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