Revealing the brain’s adaptability and the transcranial direct current stimulation facilitating effect in inhibitory control by multiscale entropy

Wei-Kuang Lianga,⁎, Men-Tzung Lo b,c, Albert C. Yang d,e, Chung-Kang Peng b,e, Shih-Kuen Cheng a, Philip Tsenga, Chi-Hung Juan a,⁎

⁎ Institute of Cognitive Neuroscience, National Central University, Jhongli, Taiwan
b Center for Dynamical Biomarkers and Translational Medicine, National Central University, Jhongli, Taiwan
c Research Center for Adaptive Data Analysis, National Central University, Chungli, Taiwan
d Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
e Division of Interdisciplinary Medicine & Biotechnology and Margret & H.A. Rey Institute for Nonlinear Dynamics in Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Accepted 23 December 2013
Available online 31 December 2013

ABSTRACT

The abilities to inhibit impulses and withdraw certain responses are critical for human’s survival in a fast-changing environment. These processes happen fast, in a complex manner, and sometimes are difficult to capture with fMRI or mean electrophysiological brain signal alone. Therefore, an alternative measure that can reveal the efficiency of the neural mechanism across multiple timescales is needed for the investigation of these brain functions. The present study employs a new approach to analyzing electroencephalography (EEG) signal: the multiscale entropy (MSE), which groups data points with different timescales to reveal any occurrence of repeated patterns, in order to theoretically quantify the complexity (indicating adaptability and efficiency) of neural systems during the process of inhibitory control. From this MSE perspective, EEG signals of successful stop trials are more complex and information rich than that of unsuccessful stop trials. We further applied transcranial direct current stimulation (tDCS), with anodal electrode over presupplementary motor area (preSMA), to test the relationship between behavioral modification with the complexity of EEG signals. We found that tDCS can further increase the EEG complexity of the frontal lobe. Furthermore, the MSE pattern was found to be different between high and low performers (divided by their stop-signal reaction time), where the high-performing group had higher complexity in smaller scales and less complexity in larger scales in comparison to the low-performing group. In addition, this between-group MSE difference was found to interact with the anodal tDCS, where the increase of MSE in low performers benefited more from the anodal tDCS. Together, the current study demonstrates that participants who suffer from poor inhibitory control can efficiently improve their performance with 10 min of electrical stimulation, and such cognitive improvement can be effectively traced back to the complexity within the EEG signals via MSE analysis, thereby offering a theoretical basis for clinical intervention via tDCS for deficits in inhibitory control.

© 2014 Elsevier Inc. All rights reserved.

Introduction

Inhibitory control reflects the ability to suppress a prepotent response and is an important cognitive ability in almost every aspect of our daily life. It requires our brain to make a fast adaptation to an ever-changing environment. For example, when a driver is ready to step on the gas pedal to accelerate (the prepotent response to a green traffic light), the sudden appearance of a child running into the lane necessitates the driver to adapt to this fast environmental change and exercise strong inhibition to stop the initiated response. In the laboratory, inhibitory control is often investigated using a stop-signal task (Logan and Cowan, 1984; Logan and Irwin, 2000), where a ‘go’ signal requires a motor response from the participants, but an irregularly-intervening sudden ‘stop’ signal requires the response to be inhibited (e.g., Aron and Poldrack, 2006; Li et al., 2006, 2008; Swann et al., 2012). To quantify the performance on the stop-signal task, behavioral data have been modeled successfully as a race between the stop and go processes to obtain a measure for estimating the time needed to inhibit a response, referred to as the stop-signal reaction time (SSRT) (Logan and Cowan, 1984). Brain signals (e.g., BOLD signal, ECoG, and EEG) acquired from essential loci/ electrodes during the stop signal task has also introduced some promising physiological measures that are related to behavioral performance (e.g., Li et al., 2006; Lo et al., 2013; Swann et al., 2009). However, beyond merely demonstrating a relationship between certain physiological measures and the behavioral performance, there is a need.
to investigate these brain signals using a measure that is able to theoretically quantify the adaptability and efficiency of neural systems during the processes of inhibitory control.

To better quantify the adaptability and efficiency of the neural signals during the stop-signal task, we calculated the multiscale entropy (MSE; Costa et al., 2002, 2005; Peng et al., 2009) of EEG signals acquired along with the stop-signal experiment. MSE, in short, is an extension of Shannon's entropy (Shannon and Weaver, 1949) and Pincus' approximate entropy (Pincus, 1991). The MSE calculates sample entropies (Richman and Moorman, 2000), a modification of approximate entropy, for biological signals by grouping data points with different timescales (coarse-grained time series). Sample entropy of each coarse-grained time series is a measure to reckon signal complexity by evaluating the occurrence of repetitive patterns. Therefore, low MSE signifies that the time series is more deterministic or regular, whereas high MSE indicates that the signal is more complex and information rich. Prior research has indicated that physical and mental illness are often related to decreased MSE in physiological signals (e.g., Catarino et al., 2011; Costa et al., 2005; Mizuno et al., 2010), whereas an increase of MSE in brain signals has been demonstrated as a critical index in development (McIntosh et al., 2008). Furthermore, previous studies have emphasized the MSE is vital to the understanding of brain mechanisms of cognition and behavior (Breakspear and McIntosh, 2011; Deco et al., 2011). Therefore, the current employment of MSE to understand inhibitory control is motivated by three basic hypotheses: 1) the complexity of a biological system reflects its ability to adapt and function in a fast-changing environment; 2) biological systems need to operate across multiple spatial and temporal scales, and hence their complexity is also multi-scaled; and 3) the "ability to adapt" by the brain for a cognitive function is associated with the neuroplasticity of this function.

Based on such understanding of the MSE, the present study also applies anodal tDCS over the preSMA to facilitate the neuroplasticity of inhibitory control (Hsu et al., 2011; Liang and Juan, 2013; for other brain stimulation results that supported an essential role of preSMA in inhibitory control, please see Chen et al., 2009; Mars et al., 2009; Neubert et al., 2010; For a review see Neubert et al., 2012), thereby investigate how the MSE values change along with the facilitating effect of anodal tDCS. Anodal tDCS has been shown to be able to temporarily increase the firing rate of cortical neurons, thereby improving the neuroplasticity of the brain region where electricity was delivered (Bindman et al., 1964). By applying anodal tDCS over the preSMA, one study (Hsu et al., 2011) has demonstrated a robust improvement that can efficiently decrease the error rate in inhibitory control. Therefore, the current study aims to go beyond the original behavioral results and analyze any event-related or tDCS-induced complexity in electrophysiological signals behind inhibitory control. To this end, the aim of the current study is threefold: 1) to compare MSE of electrophysiological signals between successful and unsuccessful stop trials; 2) to see the changes in MSE after anodal tDCS application over preSMA; and 3) to identify the MSE pattern that is associated with superior performance in inhibitory control. We hypothesize that the electrophysiological signals from successful stop trials are more complex and information rich than those from unsuccessful stop trials. We also hypothesize that anodal tDCS over preSMA will increase the MSE and improve inhibitory control. In addition, we postulate that the MSE pattern of high-performing participants is different from that of low-performing participants, at least in some specific scales.

Materials and methods

Eighteen neurologically normal adults (10 males, mean age = 25.4) participated in the experiment. Informed consent was obtained from each participant before the experiment. The experiment was approved by the Institutional Review Board of the Chang-Gung Memorial Hospital (Taoyuan, Taiwan).

Stop-signal paradigm

The stop-signal task consisted of two types of trials: go, which was signalled with an arrow, and stop, which was signalled with an arrow followed by a diamond (Fig. 1). In a go trial, each session began with a 500 ms central fixation cross, followed by a 200 ms blank screen. After the blank screen, an arrow (go signal) pointing either to the right or left was displayed, and participants were told to respond to the direction of the arrow with their corresponding index finger as soon as possible. Participants were also told that sometimes the arrow would be followed by a diamond (stop-signal) in the center of the display after a delay (stop-signal delay (SSD)), and that they should withhold their responses if the diamond appeared.

The experiment consisted of two formal sessions performed on two separate days: one with anodal tDCS over preSMA and the other with no tDCS to serve as a control condition. The two sessions were at least 24 h
Fig. 3. Grand averaged MSE pattern in scales 1–25 of both SST and USST trials in (A) No-tDCS condition, and (B) Anodal-tDCS condition. S.E.M. at each scale is indicated by the error bar.
B) SST vs. USST (Anodal-tDCS)

Fig. 3 (continued).
apart, and their order was counterbalanced across all participants. On both days, participants were also given two preliminary blocks before the formal experimental session in order to determine their choice reaction time (CRT) and critical SSD. Since each participant’s CRT and critical SSD can be readily determined with the two preliminary blocks on the first day, the blocks on the second day merely served as practice blocks and were done for the sake of consistency between the two days. Thus, the entire procedure (two preliminary blocks and one formal session) was identical between the two days, except for tDCS (Anodal-tDCS vs. No-tDCS). On the day of the formal anodal tDCS session, participants received anodal tDCS over preSMA for 10 min after the second preliminary block and before the formal session.

To determine each participant’s CRT, the first preliminary block consisted of 80 go trials, and the individual-specific mean CRT and standard deviation from this block were used to monitor participants’ performance in the subsequent block and formal session. Thus, the first block gave each participant an individually tailored timeframe for the go signal for the following sessions so that the timeframe was neither too easy nor too difficult. If a participant’s CRT on any trial in any of the subsequent sessions was two standard deviations longer than their mean CRT from this block, they received visual feedback saying “You did not press the button fast enough” to serve as a reminder to press the button as soon as the arrow appeared. This procedure has been demonstrated to effectively limit the strategy of intentionally slow responses that participants sometimes use to avoid errors (Chen et al., 2009; Muggleton et al., 2010; for a review see Juan and Muggleton, 2012).

In the second preliminary block, 90 go trials and 30 stop trials were presented. The initial SSD was set at 200 ms, and gradually moved lower or higher as the algorithm tracked the participant’s success rate. If the participant’s response in a stop trial was correct, the level of difficulty of the next stop trial would be increased by adding 50 ms to the SSD. If the participant’s response was incorrect, the SSD in the next stop trial would be reduced by 50 ms. At the end of this block, a critical SSD for each participant was obtained via this tracking method, which gives an overall inhibition probability of approximately 50% in every individual.

Finally, the formal experimental session on both days was conducted in 3 identical blocks, each lasting approximately 7 min. This was done so that participants could have a short break at around the same time interval. In each of these blocks, three types of SSDs were used: 50 ms less than the critical SSD (SSD1; an easier condition), critical SSD (i.e. SSD2), and 50 ms more than the critical SSD (SSD3, a harder condition). There were 40 trials for each type of SSD, all randomized and interleaved within every block, resulting in a total of 120 trials every block. This randomized and interleaved design was used here because it minimizes the possibility of participants’ different speeds for each type of trial.

tDCS protocol

A Neuroconn Eldith DC-stimulator with saline-soaked sponges (4 × 4 cm) was employed to deliver tDCS over preSMA. The stimulation site for the preSMA was localized with the EEG 10–20 system, with the center of the anodal tDCS electrode placed over the site of Fz. The reference electrode was positioned on the left cheek of each participant (Hsu et al., 2011). The current was applied for 10 min with an intensity of 1.5 mA. Both the current density and the stimulation strength were well below the safety criterion proposed by Nitsche et al. (2003).

EEG recording

EEG was continuously recorded with 62 Ag/AgCl electrodes mounted on a plastic cap (NeuroScan Synamp2). The sampling rate was 1000 Hz, with an analog 0.05–70 Hz bandpass filter. The reference was placed between channel Cz and CPz and the ground electrode was placed between FPz and Fz. Additionally, two sets of bi-polar electrodes were placed on the upper and lower side of the left eye and on the canthi of both eyes to measure vertical (VEOG) and horizontal (HEOG) eye-movements. Impedances of all electrodes were below 5 kΩ.

Preprocessing

A correction for eye-blinks was first applied to the EEG data acquired, with eye-blink peaks derived from VEOG by means of regression and correlation. All channels were re-referenced off-line to the average of the two mastoids (M1 and M2). The onset of the stop-signal was set as the zero point, and epochs ran from ~1000 to 500 ms. Artifact rejection was performed to exclude trials with EEG amplitude > ±150 µV, and EOG amplitude > ±50 µV. A low-pass filter with cutoff frequency at 70 Hz was applied to the epoched data.
MSE analysis

The MSE analysis on time scales 1–25 was performed from 400 ms prior to and 135 ms following the stop-signal, and was calculated in two steps. First, the algorithm progressively down-samples the EEG time series \( \{x_1, \ldots, x_i, \ldots, x_N\} \) for each trial in each condition. For timescale \( \tau \), the coarse-grained time series \( \{y(\tau)\} \) is obtained by averaging data points within non-overlapping windows of length \( \tau \). Therefore each element of a coarse-grained time series, \( j \), is calculated according to:

\[
y_j(\tau) = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad 1 \leq j \leq \frac{N}{\tau}.
\]

Second, the algorithm computes the sample entropy for each coarse-grained time series. Sample entropy is defined by the negative natural logarithm of the conditional probability that a time series of length \( (N/\tau) \), having repeated itself within a tolerance \( r \) (similarity factor) for \( m \) points (pattern length), will also repeat itself for \( m + 1 \) points, without allowing self-matches. In the current study, the pattern length, \( m \), was set to 1; that is, one data point was used for pattern matching. The similarity factor, \( r \), was set to 0.30; that is, data points were considered to be indistinguishable if the absolute amplitude difference between them was \( \leq 30\% \) of the standard deviation of the time series. In addition, since prior research has suggested that data lengths of \( 10^m \) to \( 20^m \) (\( m \): pattern length) should be sufficient to estimate approximate entropy (Pincus and Goldberger, 1994) or sample entropy (Richman and Moorman, 2000), estimation of sample entropy in the current coarse-grained EEG data (before the coarse-graining procedure, 535 time points) may be sufficient for \( m = 1 \) with scales 1–25.

Data preprocessing was performed using SPM8 and custom MATLAB (MathWorks) scripts. The algorithm of MSE analysis can be found at http://www.psynetresearch.org/tools.html.

Statistical method

A cluster-based non-parametric permutation (CBnPP) test (Groppe et al., 2011; Maris and Oostenveld, 2007) was employed to test the differences of multi-channel MSE between two conditions or groups. Originally, this method was used to provide weak family-wise error rate (FWER) control for EEG- and MEG-data by grouping test results

Fig. 5. (A and B) Contrast of MSE between SST and USST trials in the No-tDCS and Anodal-tDCS condition, respectively. For each scale, the EEG channels enclosed by dark red circles denoted that the difference of sample entropy between SST and USST trials on these channels were significant \( (p < 0.05, n = 18, \text{two tailed CBnPP test}) \). (C and D) Contrast of MSE between the Anodal-tDCS and No-tDCS condition for SST and USST trials, respectively. For each scale, EEG channels enclosed by dark green circles denoted that on these channels the sample entropy of the Anodal-tDCS condition was significantly higher than the No-tDCS condition \( (p < 0.05, n = 18, \text{upper tailed CBnPP test}) \).
at nearby sensors and time points into clusters based on their statistical significance and proximity. The current employment of this method is by grouping the test results of MSE at nearby sensors and scales into clusters. In this study, two EEG sensors were identified as neighbors if the distance between both was less than 40 mm, and 3000 permutations were performed for each test. This method has the advantage of protecting the multiple comparison errors, yet it is powerful (less conservative, in comparison with the Bonferroni or false discovery rate correction) to reveal significant effects, especially for the clustered effect like that from EEG data, as well as the MSE results of EEG signals.

Results

Behavior results: improved performance with Anodal tDCS over preSMA

We observed improved inhibition performance in the tDCS condition, which replicated the findings by Hsu et al. (2011). The results showed that the error (non-cancelled) rates of stop trials were significantly reduced by anodal tDCS [2-way repeated measures ANOVA on tDCS (No-tDCS and Anodal-tDCS) and SSD (SSD1, SSD2, and SSD3), n = 18; tDCS main effect: F(1,17) = 6.264, p = 0.023; SSD main effect: F(2,34) = 285.372, p < 10^{-4}; without significant interaction between SSD and tDCS: F(2, 34) = 0.051, p = 0.951, see Fig. 2]. While the index of inhibitory control performance—SSRT was significantly reduced by anodal tDCS (paired t-test, two tailed, n = 18, p = 0.0096), the accuracy on go trials, and RT of both go and unsuccessful-stop trials remained unchanged (Table 1). These data confirmed the facilitating effect of the anodal tDCS in inhibitory control.

For the following MSE analysis, we further divided these stop trials into successful-stop (SST) and unsuccessful-stop (USST) trials.

**MSE within-subject study (successful vs. unsuccessful stop trials, Anodal-tDCS vs. No-tDCS condition)**

The 62-channel EEG signals, acquired along with the stop-signal experiment, were analyzed by the MSE algorithm from scales 1 to 25. Fig. 3 showed the MSE pattern of both SST and USST trials on 15 representative EEG channels in both the No-tDCS (panel A) and Anodal-tDCS (panel B) conditions. To reveal the pattern differences amongst these conditions, repeated measures three-way analyses of variance (ANOVA) that included the factors of “Inhibition” (successful vs. unsuccessful-stop), “SCALE” (25 scales), and “tDCS” (No-tDCS vs. Anodal-tDCS) as three within-subject factors were conducted on the MSE of brain signals from each EEG channel [Fig. 4, EEG channels enclosed by a dark green circle indicated that the main effect or
interaction on this channel survived under correction of false discovery rate (FDR) (Benjamini and Hochberg, 1995) at level less than 0.05 over all EEG channels. The results showed significant main effects of “Inhibition” on EEG channels over brain regions from middle and superior frontal to parietal gyri, significant main effects of “SCALE” over all EEG channels, and a significant main effect of “tDCS” over FCz. These results indicated that the magnitude of MSE differed between the SST and USST trials, and the anodal tDCS induced a change of MSE from FCz. The ANOVAs also revealed significant “Inhibition-by-SCALE” interactions over EEG channels from frontal to parietal brain areas, significant “SCALE-by-tDCS” interactions on some EEG channels over superior frontal brain region, but no “Inhibition-by-tDCS” interaction, indicating that the MSE pattern of SST trials was different from that of USST trials, and the anodal tDCS effect on the MSE varied between scales.

Instead of using traditional post-hoc tests, the CBnPP test was employed both to further elucidate the pattern differences of MSE between each pair of conditions following the inferences from the ANOVAs, and to reveal clustered effects along the entire channels × scales space. We tested for difference in MSE between the SST and USST trials, and these contrasts (as t values), both in the No-tDCS and Anodal-tDCS conditions, are shown in Figs. 5A and B, respectively. For each scale, the EEG channels enclosed by dark red circles denote that on each of these channels the difference of sample entropy between SST and USST trials was significant (p < 0.05, n = 18, two tailed CBnPP test). In the No-tDCS condition for scales from 1 to 4, the MSE of the EEG channels over the frontal lobe were higher for SST than USST trials. Along with the enlargement of the scale, the effect of higher entropy for SST vs. USST trials extended to the parietal lobe, and might include the occipital lobe as scale larger than 10. In the Anodal-tDCS condition, the difference between SST and USST trials was similar to the No-tDCS condition, but with smaller cluster-extent of this effect.

We further tested whether the MSE in the Anodal-tDCS condition was greater than the one in the No-tDCS condition, both for SST and USST trials. For SST trials, the contrast of MSE, between the Anodal-tDCS and No-tDCS condition, showed that the MSE in the Anodal-tDCS condition was not significantly higher than the No-tDCS condition (n = 18, upper tailed CBnPP test, shown in Fig. 5C). Conversely, for USST trials, the contrast of MSE between the Anodal-tDCS and No-tDCS condition revealed significant increases of MSE after anodal tDCS application (p < 0.05, n = 18, upper tailed CBnPP test, shown in Fig. 5D).

To account for the above contrasts between each pair of conditions, a simple MSE scheme of tDCS facilitating effect on inhibitory control is proposed here and depicted in Fig. 6. This scheme is based on three assumptions: 1) for each participant, there exists a threshold region of...
MSE between the SST and USST trials; 2) although the anodal tDCS may increase the MSE of SST trials, the increase of MSE is limited; that is, there is an upper limit for MSE; 3) anodal tDCS will globally increase the MSE of USST trials such that the MSE of a portion of these trials, whose MSE were originally below the threshold region, are shifted over the threshold region and become SST trials. As an expected consequence of these assumptions, anodal tDCS should cause an increase on the ratio of trials above the threshold (SST trials), but not on the mean MSE of SST trials. Conversely, anodal tDCS should reduce the ratio of trials below threshold (USST trials), and elevate the mean MSE of these USST trials. To verify these assumptions, we further tested for USST trials to check whether the lower quartile (Q1) of MSE in the Anodal-tDCS condition was higher than that of the No-tDCS condition, and for SST trials whether the upper quartile (Q3) of MSE was greater for the Anodal-tDCS vs. No-tDCS condition. The testing results support the proposed scheme (for more details, see Inline Supplementary Figs. S1, A and B).

Inline Supplementary Fig. S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.12.048.

MSE pattern between-group study (high- vs. low-performing participants)

The findings in the previous subsection suggest that inhibitory control benefits from a higher MSE, which was validated within each participant’s own MSE space. However, in addition to the within-subject comparisons above, it is also essential to examine between-subject differences of MSE pattern. Therefore, we sorted the 18 participants by their SSRT in the No-tDCS condition, and divided the participants...
into a high-performing (SSRT: 175.04–196.70 ms, 9 participants) and low-performing (SSRT: 203.24–236.94 ms, 9 participants) group. The MSE patterns of stop trials (the MSE of SST and USST trials were averaged for each participant to collapse one within-subject factor. According to the assumptions depicted in Fig. 6, this averaging will keep, but may dilute the effect of anodal tDCS) of both groups, both in the No-tDCS and Anodal-tDCS conditions, are shown in Figs. 7A and B, respectively. Interestingly, the high-performing group indeed showed a different pattern of MSE from the low-performing group, both in small (≤ 8) and large (≥ 18) scales—but mutually in reverse direction.

To verify the pattern difference between the high- and low-performing group, mixed three-way analyses of variance (ANOVA), with “Group” (high- vs. low-performing) as a between-subject factor, and “scale range” (SR) (small-scale: 1–8, medium-scale: 9–17, and large-scale: 18–25; obtained by averaging the MSE across scales within each of the three scale range) and “tDCS” (No-tDCS vs. Anodal-tDCS) as two within-subject factors, was conducted on the MSE of brain signals from each EEG channel (Fig. 8, EEG channels enclosed by a dark green circle indicated that the main effect or interaction on this channel survived under FDR control at level less than 0.05 over all EEG channels). The ANOVAs showed significant SR main effects over all EEG channels and a significant tDCS main effect over FCz, but no effect of group. Importantly, the ANOVAs revealed significant Group-by-SR interactions over all EEG channels, providing the first piece of evidence of the MSE pattern difference along the scale factors between the high- and low-performing group. The ANOVAs also showed significant Group-by-tDCS interactions on CP channel-cluster (from CP3 to CP4, and P2). This indicates that although the anodal tDCS seems to increase the MSE over fronto lobe across most of the participants, the increases differ in its extension to parietal lobe between the two groups.

To further elucidate the pattern differences of MSE between the two groups as well as clustered effects along the channels × scales space, a two-sample CbnPP test was employed in what follows. Firstly, we tested whether the MSE with scales within the small-scale range were higher for the high-performing group in comparison to the low-performing group. In the No-tDCS condition, the result confirmed that within the small-scale range the MSE of the high-performing group were significantly higher than that of the low-performing group (p < 0.05, degree of freedom (df) = 16, upper tailed, shown in Fig. 9A). However, in the Anodal-tDCS condition, the higher effects of MSE within the small-scale range for high- vs. low-performing group were not significant (df = 16, upper tailed, shown in Fig. 9B), indicating that the efficiency of anodal tDCS may differ between the high- and low-performing group. Secondly, we tested whether the MSE with scales within the large-scale range were lower for the high-performing group as compared to the low-performing group. In both No-tDCS and Anodal-tDCS conditions, the result confirmed that the MSE of the high-performing group were significantly lower than those of the low-performing group (p < 0.05, df = 16, lower tailed, shown in Figs. 9C and D), together with the finding in the previous subsection that the anodal tDCS was not able to significantly influence the MSE from scales 18 to 25, we conclude that the large-scale effects are perhaps difficult to be altered with anodal tDCS. Regarding the MSE with scales within the medium-scale range, since no significant cluster of differences between both groups (p > 0.05, df = 16, lower tailed) were found, the results are not shown here.

Two additional CbnPP tests were further performed to identify the anodal tDCS effects on MSE from scales 1 to 25 within the low- and high-performing groups separately. For the low-performing group, the result revealed that the MSE in the anodal-tDCS condition were significantly higher than that in the No-tDCS condition (see Inline Supplementary Fig. S2A), and the tDCS effect on MSE extending from the frontal lobe to the parietal lobe. Conversely, for the high-performing group, the result showed that the MSE were not significantly higher for the anodal-tDCS vs. No-tDCS condition (see Inline Supplementary Fig. S2B), and the limited tDCS effect was confined to the EEG channels over the frontal lobe. This explained the significant Group-by-tDCS interactions in the ANOVAs on the EEG channels over the parietal lobe. Due to the unbalanced tDCS effect between the low and high performers, the distances of small-scale MSE between the high- and low-performing group were narrower in the Anodal-tDCS as compared to the No-tDCS condition, consistent with the results shown in Figs. 9A and B. See Inline Supplementary Fig. S3 which showed that the decreasing effect of anodal tDCS on SSRT was significant in the low-performing group (paired t-test, t(8) = 4.8226, p = 0.0013), but not in the high-performing group (paired t-test, t(8) = 0.6678, p = 0.5231), serving as a behavioral parallel with the MSE result.

Inline Supplementary Figs. S2 and S3 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.12.048.

Discussion

The present study employed the MSE analysis to theoretically quantify the adaptability and efficiency of neural systems during the process of inhibitory control. We found that the complexity of EEG signals was higher for successful than unsuccessful inhibition, and that anodal tDCS over preSMA increased the complexity of EEG signals along with its behaviorally facilitating effect. In addition, the current study also demonstrated different MSE patterns between the high- and low-performing group in inhibitory control. To our knowledge, this is the first study that employed the MSE both to distinguish between successful and unsuccessful inhibition, and to account for the effect of brain stimulation in human cognition.

Methodological considerations

Nonstationarities in signals may substantially alter the MSE results (Costa et al., 2005, 2007). However, prior research has demonstrated that the trend that causes nonstationarity of signals can be removed by applying the empirical mode decomposition (EMD) (Costa et al., 2007; Ho et al., 2011; Huang et al., 1998). Before we wrote this manuscript, we had two versions of the results; one was from MSE only, and the other was from “EMD + MSE”. The two results were similar with each other; that is, both converged to the same conclusions and inferences for the MSE differences between SST and USST trials, as well as the effect of tDCS on MSE. Afterward we decided to conclude our study by using the MSE itself, because 1) we wanted to keep the methods simple, provided that the results were consistent with that from the EMD + MSE version; and 2) the time window we used to calculate MSE is short (535 ms) and the MSE always centralizes the data before calculating the sample entropy, therefore, the data in the time window is approximately “locally stationary”.

Successful vs. unsuccessful stops

The within-subject results revealed that the brain activity of the SST trials was more complex and information rich than the USST trials. This indicated that in SST trials the ability of adaptation to environmental change was higher in comparison to USST trials, thereby allowing the brain to successfully adapt to an irregularly-intervening sudden ’stop’ signal. Anodal tDCS significantly increased the mean MSE from scales 1 to 17 over the frontal lobe for USST trials, but had no effect on the mean MSE for SST trials. These within-subject effects of MSE, together with the tDCS facilitating effect on behavioral performance, converged to a MSE scheme (Fig. 6) that can account for all the MSE and behavioral within-subject results. In this scheme, the mean MSE was higher in SST trials than USST trials, and a threshold region of MSE lay between the SST and USST trials. Furthermore, this scheme also depicted that anodal tDCS can result in an overall increase of MSE for most trials and therefore causing a higher ratio of trials with MSE above the threshold region, which may be the reason for the improvement in behavioral performance (reduced non-cancelled rate/higher ratio of SST trials). Note
A) High vs. Low performers (No-tDCS)

Sample entropy

Scale factor

C3 Cz C4

CP3 CPz CP4

P7 Oz P8

High

Low
B) High vs. Low performers (Anodal-tDCS)

Fig. 7. Grand averaged MSE pattern of stop trials of both the high- and low-performing groups in (A) No-tDCS condition, and (B) Anodal-tDCS condition. S.E.M. at each scale is indicated by the error bar.
that the threshold region of MSE between SST and USST trials is an overlapped region, and in general there is not a clear-cut division. This is reasonable for the current MSE analysis of EEG signals, since the EEG signal was an entanglement of various brain sources, including both task-related and task-unrelated sources. Therefore, future studies that can identify a clear-cut or narrower threshold region of MSE between SST and USST trials by untangling brain signals (e.g. electrocorticography (ECoG)) from inhibitory control related brain regions would be very fruitful.

Individual differences, brain stimulation, and MSE

Furthermore, by dividing participants into a high- and low-performing group based on their SSRT, the present study demonstrated that the high-performing group can be characterized by higher complexity within small-scale ranges (1–8), as well as lower complexity within large-scale ranges (18–25). Consequently, the MSE patterns of both groups intersected approximately between scales 11 and 13. The MSE pattern difference between the high- and low-performing group is similar to the difference between healthy subjects and Alzheimer’s disease (AD) patients proposed in a 2010 study by Mizuno et al. The previous MSE study for AD patients suggested that the increased complexity at large-scale range in AD reflects abnormal neuronal network connectivity, interpreted as a disconnection syndrome (Delbeuck et al., 2003). Since all participants were neurologically normal in the current study, we are not able to infer that the increased complexity at large-scale range in low-performing group is specifically related to abnormal neuronal network connectivity, or other general mechanisms such as poor inhibitory or attentional control. However, we do think it is reasonable to say that these low performers are likely to have used a relatively large temporal scale neurophysiological dynamics (less efficient), whereas high-performing individuals tend to employ a smaller temporal scale neurophysiological dynamics, to deal with an irregularly environmental change in inhibitory control.

The uneven anodal tDCS effect on MSE between the low- and high-performing group suggested an upper limit of efficiency in the current tDCS protocol. Before the anodal tDCS, within small-scale range, the MSE of the high-performing group were higher than those of the low-performing group over both frontal and parietal lobes. With anodal tDCS, the small-scale MSE of these high performers cannot be significantly elevated over the frontal lobe or the parietal lobe, albeit a tendency of increased MSE was observed on FCz. Conversely, for the low performers, anodal tDCS significantly increased the small- and medium-scale MSE over both frontal and parietal lobes. Thus, although anodal tDCS in theory should result in facilitative effect in inhibitory control and in our hypothesis a consequential increase effect on MSE, its effect may very well be dependent on people’s natural ability (or baseline) to adapt to the environmental change and their natural upper limit both in behavioral performance and the MSE. Therefore, since the small-scale MSE of the high performers were already high over the frontal and parietal lobe, it is possible that anodal tDCS could not further elevate it, especially over the parietal lobe. On the other hand, because the small-scale MSE of the low-performing individuals were low over the frontal and parietal lobe to begin with, anodal tDCS was able to rapidly increase the MSE not only over the frontal lobe (where the anodal electrode was placed), but also extended its effect over the parietal lobe. A study by Tseng et al. (2012) also reported an uneven tDCS effect between low- and high-performers in a visual short-term memory task. Similar uneven efficiency can also be found in prior transcranial magnetic stimulation (TMS) research (e.g. Cotelli et al., 2008; Manenti et al., 2011; Rossi et al., 2004; Sole-Padulles et al., 2006). Note that the tDCS protocol in the present study can more efficiently enhance the ability of inhibitory control for the low-performers, but without impairing the high-performers’ inhibitory control (see Inline Supplementary Fig. S3).

The within-subject results in this study suggest that higher MSE (across scales 1–25) is related to better performance in inhibitory control, and anodal tDCS can further elevate MSE between scales 1 and 17. At first glance, this seems to contrast the between-group results that indicate lower MSE on scales 18–25 for high- vs. low-performing group. We think that perhaps each participant may have his/her own MSE space, and trials with higher MSE within the space carried richer information and could adapt to upcoming environmental change more easily. From this perspective we suggest that higher MSE leads to better performance on inhibitory control for each participant, and that anodal tDCS assists such elevation of MSE. Regarding the lower MSE between scales 18 and 25 for high performers, we think that this may be reflective of the strategy for inhibitory control that each participant has adopted (e.g. the length of temporal scale that one’s neurophysiological dynamics employed). This strategy may be formed along
Fig. 9. (A and B) Contrast of MSE within small-scale range between high and low performers in the No-tDCS and Anodal-tDCS condition, respectively. For each scale, EEG channels enclosed by dark green circles denoted that on these channels the sample entropy of the high-performing group was significantly higher than the low-performing group ($p < 0.05$, upper tailed CBnPP test). (C and D) Contrast of MSE within large-scale range between the high- and low-performing group in the No-tDCS and Anodal-tDCS condition, respectively. EEG channels enclosed by dark yellow circles denoted that on these channels the sample entropy of the high-performing group was significantly lower than the low-performing group ($p < 0.05$, lower tailed CBnPP test).
with the long-term brain development of each participant, and is hard to be altered by brain stimulations. However, in each participant’s own MSE space, the elevation of MSE remains essential for performing inhibitory control (this can be confirmed by the contrast of MSE between successful and unsuccessful trials).

From the perspective of the current study, the effect of anodal tDCS over preSMA is to increase the complexity of brain signals from EEG electrodes over frontal brain regions (especially over the superior...
frontal gyrus), and this is concurrent with the improvements in behavioral performance. This implies that a more information-rich brain activity in frontal brain regions is at least one causative factor for better performance in inhibitory control. This partially aligns with previous findings that suggested that preSMA plays a critical role in inhibitory control, both at the behavioral level (e.g. Chen et al., 2009; Hsu et al., 2011; Nachev et al., 2007) and at the physiological level (e.g. Li et al., 2006; Mars et al., 2009; Neubert et al., 2010). However, the current study demonstrated that a better performance of inhibitory control can be contributed by a more complex brain dynamics (higher MSE) within the superior frontal gyrus, in contrast with the more conventional thinking that better performance is usually related to a greater response within the brain area. This study has therefore replicated and elucidated Hsu et al.’s tDCS finding that preSMA plays a causal role in inhibitory control, while further providing an electrophysiological basis for this modulation.

Indeed, such electrophysiological basis can also provide additional explanation for previous TMS findings reporting a facilitating effect in certain cognitive tasks (e.g. Ellison et al., 2003; Fecteau et al., 2006; Silvanto et al., 2008; Walsh et al., 1998). Previous research has indicated that this kind of TMS effect may be a result of a competition between two cortical regions when their related brain functions shared common brain resources (Ellison et al., 2003). That is, when TMS virtually impaired one cortical region, the balance of the common resources shifted to the other cortical region and the brain function to which the region contributed. From the perspective of the MSE, more neural resources would correspond to richer information, and thus higher MSE would be expected. In addition, the efficacy of both TMS and tDCS in cognitive neurorehabilitation, as identified by previous studies (Berardelli et al., 2008; Bermpohl et al., 2006; Ellaway et al., 2007; Fregni et al., 2006; Meinezer et al., 2013; Minnìusi and Rossini, 2011; Minnìusi et al., 2008; Rossi et al., 2009), can also be further confirmed with the MSE during or after the period of brain stimulation treatment. It has already been demonstrated that pathologic states are associated with a loss of dynamical complexity (e.g. Costa et al., 2007; Yang et al., 2011). Therefore, therapeutic interventions that increase (or restores) physiological complexity may possibly enhance patients’ health status, and carefully-parameterized brain stimulation may be the optimal mean to achieve that.

All together, the current findings provided a theoretical basis for clinical intervention via tDCS, that is, anodal tDCS over preSMA can elevate the MSE during inhibitory control. This theoretical base may suggest a potential application of tDCS to those clinical conditions where deficits in inhibitory control are implicated, such as addictions (e.g. Bednarski et al., 2012; Li et al., 2010; Luo et al., 2013) and obesity (e.g. Hendrick et al., 2012). Therefore, future studies for the aforementioned clinical conditions may want to investigate whether decreased MSE can be observed along with deficits in inhibitory control. Another research issue with great potential is to investigate the effect of brain stimulations on cognitive function and neurorehabilitation via MSE.

Conclusion

In summary, this study utilized a new approach—the MSE—to characterize the efficiency and adaptability of neural and cognitive processing during inhibitory control. More importantly, this study also accounts for the effect of brain stimulation in inhibitory control from the perspective of MSE. Therefore, we propose that the MSE analysis, both theoretically and pragmatically, is an elaborate index that can reveal the efficiency of the cognitive neural mechanism across multiple timescales, especially for those cognitive functions requiring participant to rapidly adapt to a fast-changing event or environment. Furthermore, we suggest that these findings from MSE can serve as a theoretical basis for tDCS intervention over preSMA, and can offer a novel direction to future studies for clinical conditions where deficits in inhibitory control are implicated.

Acknowledgment

This work was sponsored by the National Science Council, Taiwan, the Veterans General Hospitals, Taiwan, and University System of Taiwan (99-2410-H-008-022-MY3, 101-2410-H-008-033-MY3, 101-2811-H-008-014, 100-2410-H-008-074-MY3, 100-2511-S-008-019, 101-2911-I-008-001, and VGHUST101-G4-1-1). We are grateful to Neil G. Muggleton and Neil Leveridge for their insightful comments on this manuscript.

Conflict of interest

None.

References


