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Rajan Kashyap, Sagarika Bhattacharjee, Ramaswamy Arumugam, Rose Dawn Bharath ...+5 more authors

Institutions: Nanyang Technological University, National Institute of Mental Health and Neurosciences, Johns Hopkins University School of Medicine

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Rajan Kashyap[1*], Sagarika Bhattacharjee[2], Ramaswamy Arumugam[3], Rose Dawn Bharath[4], Kaviraja Udupa[5], Kenichi Oishi[6], John E. Desmond[6†], SH Annabel Chen[2,3,7,8#], Cuntai Guan [1*#]

[1] School of Computer Science and Engineering, Nanyang Technological University, Singapore
[2]Psychology, School of Social Sciences (SSS), Nanyang Technological University, Singapore
[3]Centre for Research and Development in Learning (CRADLE), Nanyang Technological University, Singapore
[4]Department of Neuroimaging and Interventional Radiology, National Institute of Mental Health and Neurosciences, India
[5]Department of Neurophysiology, National Institute of Mental Health and Neurosciences, India
[6]The Johns Hopkins University School of Medicine, Baltimore, United States
[7]Lee Kong Chian School of Medicine (LKC Medicine), Nanyang Technological University, Singapore
[8]National Institute of Education, Nanyang Technological University, Singapore

# Equal contribution, †senior author

Address correspondence to:
Rajan Kashyap
School of Computer Science and Engineering
Nanyang Technological University, Singapore
Email: rajankashyap6@gmail.com

And

Cuntai Guan
School of Computer Science and Engineering
Nanyang Technological University, Singapore
Email: ctguan@ntu.edu.sg

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Abstract

Background: In Transcranial Direct Current Stimulation (tDCS) the injected current gets distributed across the brain areas. The motive is to stimulate the target region-of-interest (ROI), while minimizing the current in non-target ROIs. For this purpose, determining the appropriate current-dose for an individual is difficult.

Aim: To introduce Dose-Target-Determination-Index (DTDI) to quantify the focality of tDCS and examine the dose-focality relationship in three different populations.

Method: Here, we extended our previous toolbox i-SATA to the MNI reference space. After a tDCS montage is simulated for a current-dose, the i-SATA(MNI) computes the average (over voxels) current density for every region in the brain. DTDI is the ratio of average current density at target ROI to the ROI with maximum value (peak region). Ideally target ROI should be the peak region, so DTDI shall range from 0 to 1. Higher the value, the better the dose. We estimated the variation of DTDI within and across individuals using T1-weighted brain images of 45 males and females distributed equally across three age groups- (a) Young adults ($20 \geq x < 40$ years), (b) Mid adults ($40 \geq x < 60$ years), and (c) Older adults ($60 \geq x < 80$ years). DTDI's were evaluated for the frontal montage with electrodes at F3 and right supra-orbital for three current doses 1mA, 2mA, and 3mA with the target ROI at left middle frontal gyrus.

Result: As the dose is incremented, DTDI may show (a) increase, (b) decrease, and (c) no change across the individuals. The focality decreases with age and the decline is stronger in males. Higher current dose at older age can enhance the focality of stimulation.

Conclusion: DTDI provides information on which tDCS current dose will optimize the focality of stimulation. DTDI recommended dose should be prioritised based on the age (> 40 years) and sex (especially males) of an individual. The toolbox i-SATA(MNI) is freely available.

Keywords: Transcranial direct current stimulation (tDCS), Realistic volumetric Approach-based Simulator for Transcranial electric stimulation (ROAST), Systematic Approach for tDCS Analysis (SATA), Current dose, Individualized tDCS, Age and Sex difference.

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Introduction

Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation technique that could alleviate symptoms of several neurological and psychiatric brain disorders [1–3]. A conventional tDCS setup consists of anode and cathode placed over the scalp (referred as montage) with low intensity of current (~ 1- 3mA) being injected to stimulate the target region of interest (ROI) [4,5]. However, the injected current gets diffused in the intermediary regions of the brain and might not essentially stimulate the target ROI with desired intensity [6,7]. Computational models that predict the pattern of current flow across the brain of an individual are used to optimize the tDCS stimulation parameters [8–14]. The amount of injected current (referred as 'current dose') plays an important role in the dispersal of stimulation intensity across the brain regions [15,16]. The distribution may vary from person to person and within a person based on the quantity of the dose [17–19]. Therefore, selection of optimal current dose for an individual's brain that could sufficiently stimulate the target ROI while minimizing the current in non-target ROIs is important [15,16].

In recent years there has been a growing interest towards individualization of current dose [15,16,20]. It has been reported that varying the current intensity at scalp for each individual can reduce the interindividual variability in the electric field intensity at the target ROI [20]. The current dose calculated through inverse modelling of tDCS induced electric field at the target ROI correlates with the motor thresholds generated by transcranial magnetic stimulation [15,16]. In a recent tDCS experiment using frontal montage and 2mA (fixed) current dose, individuals with high simulated current density at the target ROI (left dorsolateral prefrontal cortex) were found to have stronger improvements in working memory compared to those with low current density [21]. They also showed that individualizing the current dose by fixing the current density desired at the target region can

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maximize the benefits of tDCS [21]. Though the models are a step towards individualizing the current dose, they do not consider the spread of the field to intermediary (non-target) regions. The current flow in the intermediary regions have a vital role to play in determining the outcome of tDCS [6,12,22–25]. It has been found that some brain regions may act as conduit clustering most of the current to a specific location that can deter the stimulation intensity expected at the target ROI [6,26]. Increasing the focality of stimulation in conventional tDCS setup has been an area of investigation [27–30]. Therefore, the approaches to individualize the current dose should consider the focality of stimulation in order to recommend the optimal intensity of input current.

In our previous work, we developed individual-Systematic-Approach-for-tDCS-Analysis (i-SATA) toolbox [31] that estimates the average current density received by target ROI and intermediary regions of an individual's brain after a montage has been simulated in Realistic-volumetric-Approach-based-Simulator-for-Transcranial-electric-stimulation (ROAST) toolbox [10]. We demonstrated the ease with which i-SATA toolbox can be applied on an individual brain to reverse calculate the current dose that can stimulate the target ROI with desired intensity [31]. This was done based on the assumption that electric field intensity at target ROI increases linearly with current dose by following the procedure laid down by Evans and colleagues [20] . Since we will be using it throughout the study, it will be helpful to familiarize our readers with an example. Suppose the calculated stimulation intensity at the target ROI is 0.25 mA/m^2 when 1 mA of current is applied on the scalp. To achieve an intensity of 0.5 mA/m^2 desired at the target ROI, the required dosage (individualized) can be reverse calculated as $Individualised\ dose = \left(\frac{Desired\ Intensity}{Actual\ intensity}\right) \times Fixed\ dose$ [$i.e., \left(\frac{0.5}{0.25}\right) \times 1 = 2$ mA].

In i-SATA, we used the Talairach client toolbox [32] to map an individual brain to the Talairach atlas space [33]. In this respect, another widely used brain template that provides

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detailed stereotaxic information on the location and variability of cortical areas is provided by the Montreal Neurological Institute (MNI) reference space [34–38]. Simon and colleagues [39–41] had developed the SPM anatomy toolbox that integrates the cytoarchitectonic maps in the MNI space. Here we leveraged on the potential of SPM anatomy toolbox to extend i-SATA to the MNI space. The extended toolbox i-SATA(MNI) that integrates the SPM anatomy toolbox with i-SATA will enable researchers to visualize the comprehensive overview of the current density distribution across the cortex (target and intermediary regions) in the MNI space.

With i-SATA(MNI), we introduce the *Dose-Target-Determination-Index* (DTDI), a simple estimate that will quantify the focality of stimulation and facilitate the selection of optimal current dose required to stimulate the target ROI in an individual's brain. The index provides a comprehensive overview of the intensity of stimulation received by the target ROI and intermediary regions after a montage has been postprocessed in i-SATA(MNI). To explain DTDI, we will use the montage with anode positioned at F3 and cathode at right supra-orbital (RSO) (referred to as F3-RSO, Figure 1A). The montage has been shown to stimulate the left middle frontal gyrus [22,25] and is effective for depression [3,22,42] and working memory [43]. To make it easy for our readers to interpret how DTDI facilitates selection of the current dose, we will show the inter-individual as well as the intra-individual variation in the index by uniformly increasing the current dose. Finally, we will evaluate the variation in DTDI with age and sex of individuals. The purpose will be to explore if dose selection should be prioritised for any category (age and sex) of individuals.

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Methods

Data

We obtained the T1-weighted (T1WI) magnetic resonance image (MRI) of the brain of 90 age-sex matched healthy individuals (45 male) from Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study (available at http://www.mrc-cbu.cam.ac.uk/datasets/camcan/, [44,45]). The T1WIs were collected from a 3T Siemens TIM Trio scanner with a 32-channel head coil using MPRAGE sequence, TR= 2250 milliseconds (ms), TE=2.99 ms, flip angle = 9^0, Voxel size= 1 × 1 × 1 mm^3, FOV = 256 × 240 × 192 mm^3, GRAPPA: 2; TI: 900 ms. We selected 90 T1WIs from the following three age groups with 30 individuals (15 right handed males and females) in each group – (a) Young adults ($20 \geq x < 40$ years), (b) Mid adults ($40 \geq x < 60$ years), and (c) Older adults ($60 \geq x < 80$ years) were selected. The equal grouping across the three groups would allow evaluation of the relationship of tDCS current dosage with sex and age.

Preprocessing with ROAST

We simulated the montage F3-RSO with the electrode size 5 × 5 cm^2 (Figure 1A). For each individual MRI, the montages were simulated for three current doses 1mA, 2mA, and 3 mA. In total, 270 simulations were performed in ROAST ($\text{Total} = 90\ \text{MRI} \times 3\ \text{current doses} = 270$) [10]. Default conductivity values of the tissues (white matter (default 0.126 S/m); grey matter (default 0.276 S/m); cerebrospinal fluid (default 1.65 S/m); bone (default 0.01 S/m); skin (default 0.465 S/m); air (default $2.5e^{-14}$ S/m); gel (default 0.3 S/m); electrode (default $5.9e^7$ S/m) were used for each MRI simulated in ROAST. The ROAST simulation outputs the locations (x, y, and z coordinates) of the brain regions and the current density (mA/m^2) value at each location in the native space.

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i-SATA(MNI)

The i-SATA(MNI) is similar to i-SATA [31] except for the atlas space. In short, for each montage simulated in ROAST, i-SATA extracts the location (x, y, and z coordinates) of all the points in the cortex to detect the location of three anatomical landmarks (anterior commissure, posterior commissure, and mid-sagittal) using acpcdetect toolbox [31,46]. With these landmarks, the individual's native space was mapped to the reference space (Talairach atlas space) using the fieldtrip toolbox [47] followed by Talairach client toolbox [32]. Details on the methodology and application can be obtained from previous works [11,31,48]. For i-SATA(MNI), instead of the Talairach atlas space, we mapped the outputs (x, y, and z coordinates) to the MNI reference space using the SPM anatomy toolbox [39–41]. The SPM anatomy toolbox has an option for using the gyri/sulci-based labelling system wherein the Automated Anatomical Labeling atlas with 116 regions outlined on the Colin27 brain template is implemented (for details, [49]). The i-SATA(MNI) extracts and uses the labels provided by this atlas for assigning the cortical and subcortical region corresponding to each location. A detailed explanation on the nomenclature of the delineated regions can be found at [49]. We developed i-SATA(MNI) using SPM12 (revision 6470, available at https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) that has the SPM Anatomy toolbox (version 2.2b) inbuilt in the framework. The magnitude of current density corresponding to each location (voxel) is then used to obtain the average magnitude of current density received by each cortical region of the brain. This will provide an estimate of the current density induced in the target and intermediary region due to tDCS. As an example, we will postprocess the standard MNI 152 averaged head in i-SATA(MNI) for the three current doses (1mA, 2mA, and 3mA) using the F3-RSO montage to show the distribution of average current density across the cortical regions (Figure 1B, C, D).

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Dose Target Determination Index (DTDI)

The output of i-SATA (MNI) (i.e. the average current density in the target ROI and the non-target regions) is used to calculate the DTDI for a montage simulated at a current dose. For this, we will find the ROI that has the maximum value of average current density (peak region) amongst all the ROIs. DTDI is then calculated as

$$DTDI = \frac{Average\ Current\ density\ at\ the\ Target\ ROI}{Maximum\ value\ of\ average\ current\ density\ formed\ at\ any\ ROI}$$

DTDI will lie in the range of 0 to 1. An ideal tDCS setup will expect the maximum intensity of stimulation (average current density) to be received at the target ROI, thereby generating a DTDI value equal to 1. However, the peak intensity may be received at non-targeted ROI. For an individual, the current dose for which DTDI is higher should be preferred over other doses. To make this clear, we will estimate the DTDI of three individuals across three current doses (figure 2). Hypothetically, the value of DTDI should remain constant across doses, since it is assumed that the current flow in the brain increases linearly with increase in current intensity [15,16,20,23,50].

Statistical Analysis of variation in DTDI

All individual MRIs were post processed in i-SATA(MNI) for the three current doses using the F3-RSO montage to estimate the DTDI's (Total $= 90$ MRI $\times 3$ current doses $=$ 270). We show the inter- and intra-individual variation in the DTDI for both sexes across the three age groups (Figure 3). We performed three-way mixed ANOVA with age and sex as between subject and dose as within subject factor. *Post-hoc* analysis were performed to further characterize the nature of the main effects and interactions.

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Code availability

The i-SATA(MNI) is a Linux-based-MATLAB toolbox integrating acpcdetect v2.0, fieldtrip, and SPM12 (version 6470) with integrated SPM Anatomy toolbox (version 2.2b). The package can be downloaded at (LINK_TO_BE_ADDED). A reference manual is also provided to aid users to run each step with ease.

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Results

Output of i-SATA(MNI) on the standard head model

The montage F3-RSO applied on the MNI 152 averaged head model simulated in ROAST is shown in figure 1A. The output of i-SATA(MNI) i.e. the distribution of the average current density across the cortical regions are shown in Figures 1B, C and D for the three current doses (1mA, 2mA and 3mA). The average current density in the target ROI (left middle frontal gyrus) varies linearly with the current dose. Therefore, the DTDI remains constant (approximately ~ 0.85) across the doses. Of note, similar to i-SATA [31] and SATA [11], users can visualize the i-SATA(MNI) outputs on the brain surface as well (Figure not shown).

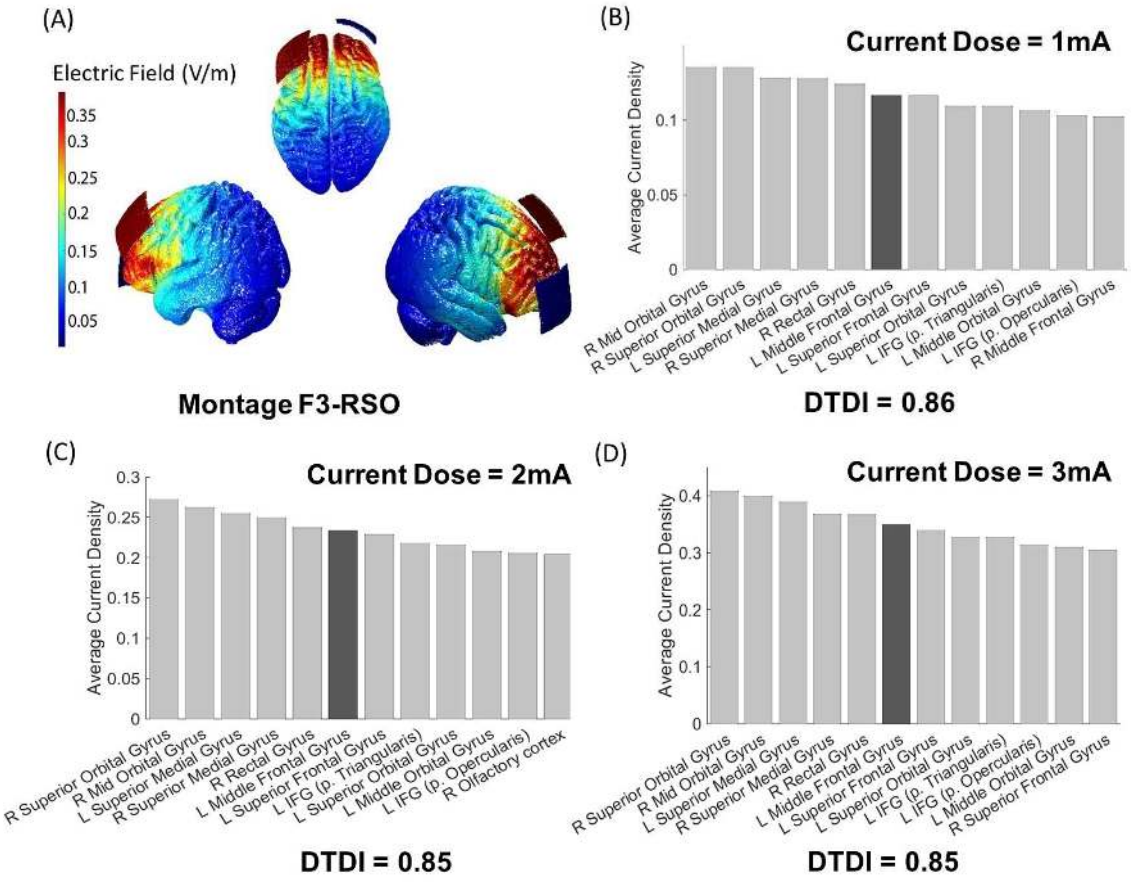

Figure 1. Illustration of the applied montage F3-RSO and output of i-SATA(MNI) for the MNI152 standard head image across the three current doses- (B) 1mA, (C) 2mA, and (D) 3mA. The average current density at the target ROI (left middle frontal gyrus) is shown in the

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dark grey colored bar. The DTDI index (~ 0.85) remains fairly constant across the 3 current doses indicating a linear relationship between the injected current and induced electric field. For the standard head, tDCS users are flexible to choose any current dose and their choice depends on the intensity of stimulation desired in the target ROI.

Interpretation of DTDI for appropriate selection of current dose

For any individual, DTDI can guide the selection of the appropriate current dose that will sufficiently stimulate the target ROI with minimal spread of current to other regions. For interpretation, we have shown the variation of DTDI for three individuals across the three current doses (Figure 2). For the first individual, the current intensity at target region increases with increase in dose and the DTDI remains fairly constant (Figure 2A). This implies that the target ROI will be sufficiently stimulated by any current dose, and the user can tune according to the extent of stimulation desired. For the second individual, a low DTDI (0.43) is seen at lower dose (1mA) suggesting that target ROI is receiving minimal current and non-target regions are receiving most of the current. With increase in dose, it can be seen that the current intensity at target-ROI is increasing but lesser number of regions are receiving current higher than the target ROI. As a result, the DTDI is increasing with increase in dose suggesting that higher current dose should be beneficial (Figure 2B). Finally for the third individual, a decrease in DTDI is seen with increase in dose (Figure 2C). The drop in DTDI from 1 mA to 2 and 3 mA seems to be due to increase in current in the right superior parietal lobule at 2 mA and 3 mA only. Although, the current intensity at target ROI is increasing with increase in dose but maximal amount of current is also getting dissipated to other brain regions. Thus, the conventional way of increasing the current dose to attain desired stimulation intensity at target ROI might result into stimulation of unwanted brain region (as seen for superior parietal lobule). For this individual, a lower dose showing higher DTDI can maximize the advantage of stimulation.

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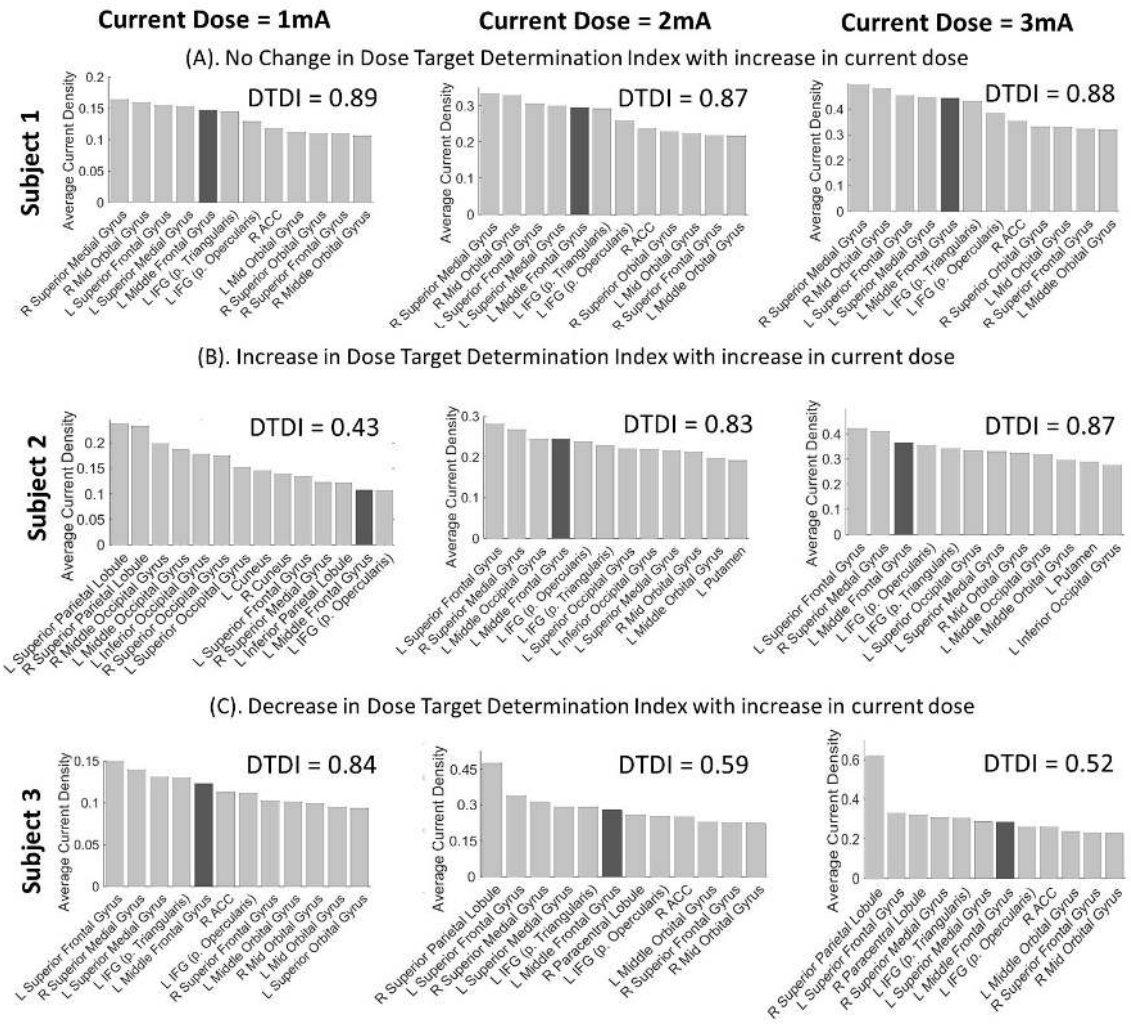

Figure 2. Illustration of the variation in DTDI for three current doses (1mA, 2mA, and 3 mA) with F3-RSO montage applied over three individuals showing (A) No change, (B) Increase, and (C) Decrease in DTDI with increase in current dose. Subject 1 with no change in DTDI is neutral to variation in current dose. Subject 2 showing increase in DTDI would receive adequate stimulation from a higher dose (above 1 mA) whereas subject 3 showing a decrease will most likely benefit from the lower dose.

Statistical Analysis of variance in DTDI

Here we will highlight the change in DTDI with increase in dose for males and females across three age groups (Figure 3). The main effect of age was significant [$F(2, 84) = 43.98$, $p < 10^{-14}$] with DTDI significantly decreasing in older adults compared to young adults ($p < 10^{-19}$). The main effect of sex [$F(1, 84) = 12.14$, $p < 10^{-04}$] and its interaction with

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age [$F(2, 84) = 3.78$, $p < 10^{-02}$] were also found to be significant. The *post-hoc* analysis shows that females had higher DTDI values than males for both mid ($p < 10^{-6}$) and older adults ($p < 10^{-3}$). The interaction effect of age and dose was also found to be significant [$F(3.34, 140.48) = 7.269$, $p < 10^{-05}$]. In older adults only, the *post-hoc* analysis revealed that there is a significant ($p < 0.05$, Bonferroni corrected) increase in the DTDI values at 3 mA compared to 1mA (for both the sexes). This shows that the focality of stimulation could be enhanced in older adults by increasing the dose.

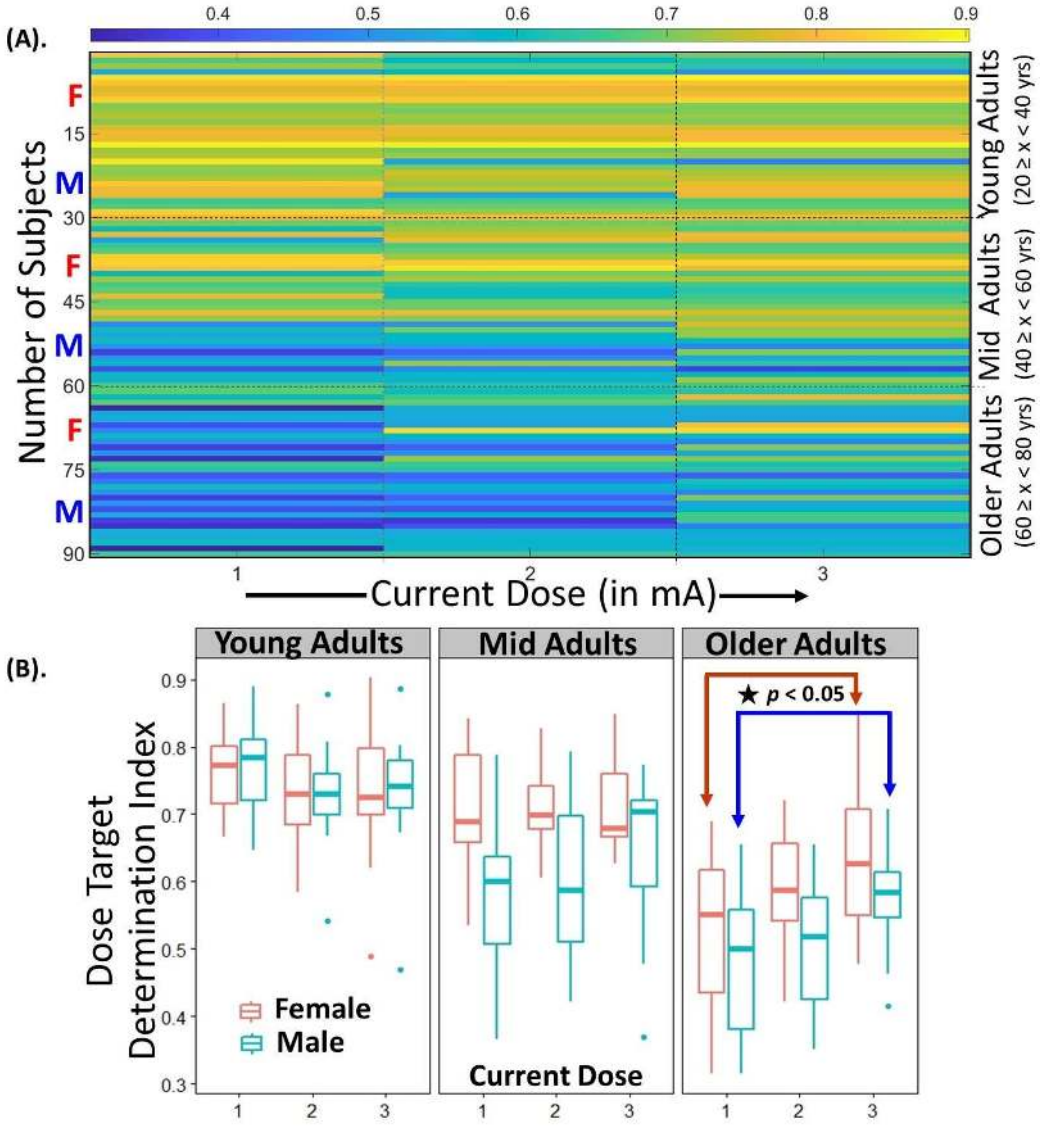

Figure 3. Illustration of the variation in DTDI at individual and group level with (A) showing the individual variation of DTDI values (0 to 1) in the females (font in red 'F') and males

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(font in blue 'M') distributed equally across the three age groups- (i) Young adults ($20 \geq x < 40$ years), (ii) Mid adults ($40 \geq x < 60$ years), and (iii) Older adults ($60 \geq x < 80$ years) for the three current doses (1mA, 2mA, and 3 mA). The inter- and intra-individual variation in DTDI clearly shows the current dose that could be appropriate for an individual to stimulate the target ROI after a montage has been fixed, and (B) showing the variation of DTDI for both sexes across the three age groups using three-way mixed ANOVA. The DTDI decreases with increase in age. In mid and older adults, females show higher focality compared to males for the three current doses (1mA, 2mA, and 3mA). In older adults only, the significant ($p < 0.05$, Bonferroni corrected) difference between DTDI at 1mA and 3 mA for both sexes conveys that higher current doses are required to appropriately stimulate the target ROI.

Discussion

In this paper, we extended the toolbox i-SATA [31] to the MNI reference space for users to obtain the average current density induced at each cortical region of an individual's brain due to tDCS. We then used these values to estimate DTDI as an objective measure to quantify the focality of stimulation and aid the selection of appropriate current dose for an individual. We demonstrated the utility of DTDI across three subjects and dose (figure 2) wherein the optimal stimulation of the target ROI in- (a) subject 1 is neutral to change in current dose, (b) subject 2 to have better focality from a dose of 2mA or more (but not from 1 mA), and (c) subject 3 to gain adequate stimulation from 1mA compared to 2 or 3mA of current dose. Such inter-individual inconsistency in tDCS due to the current dose has been widely reported in previous studies [17–19, 50–56]. With this i-SATA(MNI) framework post-processing the structural scans simulated in ROAST, tDCS users can configure personalized protocol for montage selection (refer to [11,31]) and identify the optimal current dose for cortical targeting (guided by DTDI). We applied the framework on a wide age range (20 to 80 years) of individuals from both sexes to highlight the importance of DTDI and the need for a focality-based selection of current dose.

Previous tDCS based studies have combined electroencephalography, or functional MRI, or transcranial magnetic stimulation to determine the current dose for optimal targeting [58–61]. Recently, a computational study had put forward a model to reversely calculate the

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current dose from the simulated electric field [15,16] based on the assumption that the intensity of current flow increases linearly with current dose [50]. A similar prototype was also put forward by Evans et al [20]. All these studies used young healthy subjects to delineate the model. On one hand, we see this linearity being followed in the MNI standard head model (Figure 1) and to an extent in young and middle aged individuals (Figure 2A and 3A). However, on the other hand, linearity appears to diminish with advancement in age (Figure 2B, C and 3A) suggesting a potential non-linear relationship.

The different values of DTDI as a function of current dose across different subjects could be because the injected current might get clustered in brain areas (referred as hotspots), a phenomenon that has been widely reported in tDCS studies [6,25,26,62–64]. Hotspots cause shunting of the current towards the surrounding brain tissue and a surge in the electric field strength at localised areas [65]. Areas that form hotspot can be away from the electrode site as well [65]. In the two cases presented in figure 2 (Subject 2 and 3), superior parietal lobule appears to be the hotspot. Here it is difficult to comprehend the neuroanatomical factors that attributes to the formation of such hotspots. It has been found that tissue heterogeneities and pathological alterations (like neurodegeneration and cerebral infarcts) are the primary contributors [26,65]. As we age, the atrophy in the neural configuration escalates the non-linearities in the spatial distribution of induced electric field [66,67]. Care must be taken about possibilities of such hotspots for clinical application of tDCS [68]. DTDI that considers the current density in target and non-target areas inculcates the effect of hotspots to provide a rigorous estimate of optimal current dose. However, it is important to identify the factors that contribute to observed non-linearity and alterations in DTDI in future studies.

Since maximum stimulation might not be received at the target ROI and also not in a consistent location [6,17,18,69], the inter and intra-individual variation in DTDI can provide insights for appropriate determination of current dose based on age and sex of a healthy

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individual. In young adults, the focality of stimulation remains intact (approximately) across the doses ascertaining that there is flexibility in choosing (individualising) a dose depending on the extent of current density desired at the target ROI. However, the focality declines with advancing age (middle age onwards, see Figure 3). This decline is higher for males compared to females. Such sexual dimorphism in tDCS related effects have been reported in previous studies [70] and several factors related to cortical anatomy like volume [71], bone density [72], hormonal levels [72], and electrode location [73] have been postulated to account for it. We also found that higher current dose can enhance the focality in older adults. This is in support of a recent study [74] that reported cerebral atrophy in older adults to cause the reduction in the amount of current reaching the target ROI. Altogether our findings suggest that determination of the current dose based on focality must be prioritised based on the age (> 40 years) and sex (especially males) of an individual.

We have shown the use of DTDI to titrate the current dose at the individual level. This can be done at the group level also. Evans et al [20] have suggested that the input current should be varied across individuals to maintain a constant current density at target ROI. While we agree with them, we also suggest that the focality of stimulation needs to be considered, especially when older individuals are recruited for the study. For primary clinical/therapeutic applications of tDCS, the focality as revealed by DTDI could be especially useful for setting tDCS dosage. Although compliability of the patient with the computationally recommended dose is always important [75], recent studies have indicated that participants readily tolerate tDCS current up to 4 mA [76,77].

In group studies in which researchers do not want to vary the current from subject to subject, DTDI values may still be used in two different ways to improve the efficacy of the study. The first would be to include a threshold for DTDI (e.g., DTDI ≥ 0.75) as a precautionary measure while individualising the current dose. While this may narrow down

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the suitability of subjects, such inclusion criteria could reduce the variability of tDCS. The second would be to use DTDI analyses for the populations under study to determine – at the start of the study – the optimal value of tDCS current dose to be used on all subjects that will produce the greatest focality and least amount of subject-subject variability in DTDI. For example, the current study suggests that for the F3-RSO montage if you are including older and younger subjects, a higher current value (for the study overall) might produce the least variability in terms of focality of tDCS.

Finally, we would like to highlight that DTDI can be estimated from i-SATA as well. However, simulation in i-SATA(MNI) is considerably faster than in i-SATA. This is because both i-SATA(MNI) and the integrated SPM anatomy toolbox for cortical labelling are MATLAB based and automated. This makes i-SATA(MNI) efficient to post-process large data sets, a trend that is emerging in neuroscientific research.

Conclusions

The study extends the i-SATA framework to the MNI atlas space. With i-SATA (MNI), it will be easier to calculate the individualized dose as suggested in previous studies [15,16,20,21]. Here we introduce the DTDI as measure to titrate the individualized current doses and select the optimum dose that has high focality and could appropriately stimulate the target ROI in an individual. Using a montage that has been found to be optimal for DLPFC stimulation, DTDI analysis across a broad spectrum of men and women of different age groups revealed that focality decreases with advancing age, especially in males with more than 40 years of age. Finally, the study reveals that selection of current dose that increases the focality is strictly necessary for older (> 60 years) individuals irrespective of sex.

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Declaration of conflict of interest

The authors declare no conflict of interest

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