Online cathodal transcranial direct current stimulation to the right homologue of Broca's area improves speech fluency in people who stutter

Running title: Improved speech fluency by on-line tDCS

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Abstract: (248/250 words)

Aim: Previous functional imaging studies demonstrate that people who stutter (PWS) exhibit over- and under-activation of Broca's and Wernicke's areas and their right hemisphere homologues when speaking. However, it is unclear whether this altered activation represents the neural cause of speech dysfluency or a secondary compensatory activation in PWS. To clarify the functional significance of the altered activation pattern in classic language areas and their right homologues, we examined

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whether the severity of stuttering was affected when the activation of these areas was modulated by brain stimulation.

Methods: While PWS read passages aloud, we applied transcranial direct current stimulation (tDCS) using electrode montages that included an anodal or cathodal electrode placed over one of the language areas and its right hemisphere homologue, with the second electrode placed over the contralateral supraorbital region. Each participant underwent both anodal and cathodal tDCS sessions, each of which included a sham stimulation. Effects of stimulation polarity and electrode location on the frequency of stuttering were analyzed.

Results: We observed a significant interaction between polarity and location on the frequency of stuttering. Follow-up analyses revealed that a tDCS montage including the cathodal electrode over right Broca's area (RB) significantly reduced the frequency of stuttering.

Conclusion: The results indicated that stuttering severity was ameliorated when overactivation in RB was reduced by tDCS. This observation further suggests that speech dysfluency in PWS may be caused either by functional alteration in RB or by abnormal activation in speech motor control areas that are connected with RB.

Key words: Broca's area, developmental stuttering, speech, tDCS, Wernicke's area

Introduction

Developmental stuttering is characterized by dysfluent speech with involuntary repetitions, prolongations, and blocks at the levels of syllables and words [1]. Although its etiology is still unclear, converging evidence from neuroimaging studies shows that people who stutter (PWS) have significant functional abnormalities in critical brain regions for speech processing [2]. For example, several functional imaging studies demonstrated reduced activity during speech production in Broca's area (BA), i.e., the cortical center for speech production [3,4]. Conversely, the right homologue region of Broca's area (RB) showed overactivation; this finding has been highly replicated in a number of studies including a recent meta-analysis [5–7]. Furthermore, many previous studies also consistently demonstrated reduced activation in Wernicke's area (WA) and its right homologue region of Wernicke's area (RW) [8–10].

Although these findings converge into a consistent pattern regarding functional alterations in the PWS brain, the interpretation of such altered brain activation remains unclear. For instance, although overactivation in RB has been often interpreted as a compensatory mechanism for deficient activation in BA [3,11,12], it is still possible that overactivation of RB is directly responsible for stuttering speech. Since the language centers and their right homologues are directly connected to each other through association and commissural fibers [13,14], it has been difficult to discern whether over- and under-activation in these speech-related regions reflect cause or compensation of dysfunction. Further, these regions are connected with other regions, such as the supplementary motor area (SMA) and basal ganglia [15,16], which are critical structures for speech production outside the classic language territory. Thus, the functional interpretation of altered brain activation from neuroimaging studies alone is

ambiguous.

Non-invasive brain stimulation is a promising complementary tool that can be used to test hypotheses generated from functional imaging studies. Transcranial direct current stimulation (tDCS), in particular, is gaining attention, primarily due to its effects on a broad range of cognitive, perceptual, and motor functions. Weak transcranial direct currents modulate neuronal excitability in and around the stimulated site, either in a positive or negative direction, depending on the polarity of the electrodes. Although the direction of neuronal modulation may be different depending on the neuronal organization of the stimulated site, it is often interpreted that stimulation with an anodal electrode enhances excitability of the neural tissue, whereas that with a cathodal electrode is inhibitory, at least in the primary motor cortex [17]. Previous studies have examined effects of neuronal modulation by tDCS on language processing for healthy and clinical populations. For healthy volunteers, several lines of positive evidence have been reported, including facilitatory effects on language production for words and sentences as well as language learning [18–20]. Although some studies raised the possibility that the effects of tDCS on language production actually might be small for healthy volunteers [21,22], a number of clinical tDCS studies have reported facilitation effects on impaired language functions in aphasic patients. In particular, positive effects on speech production and word retrieval on non-fluent type of stroke aphasia have been reported by several tDCS studies that involved either BA or WA as a stimulation site [23,24]. Significant tDCS effects have been identified also in primary progressive aphasia by showing facilitatory word retrieval [25]. Some of these studies have been successful in retaining the facilitatory effects over several weeks or even months after stimulation periods [24–26]. Nonetheless, the effects of tDCS on language in aphasia

patients may be variable among studies. tDCS includes several parameters that critically affect the outcome, such as the polarity of stimulation and sites of the electrodes; therefore, it is important to systematically search for the optimal combinations of these parameters to establish the effects of tDCS on language [27].

A recent study demonstrated an impressive effect of tDCS on speech fluency in developmental stuttering. Chesters and colleagues adopted a montage of an anode electrode on the left inferior frontal cortex together with a cathode electrode on the contralateral supra-orbital ridge and examined the offline effect of tDCS while PWS performed choral speech over 5 days of intervention [28]. Speech improvement was observed after 20 min of 1-mA stimulation session on each day of the intervention, and the effect was maintained up to 6 weeks after the intervention. However, to date, the effects of online stimulation to the BA and other speech-related areas (e.g., RB, WA, and RW) on speech fluency have not been tested using multiple combinations of sites and polarities of tDCS.

In the current study, we applied tDCS while PWS spoke and examined whether neuromodulation of each of the speech-related cortical sites lead to changes in speech fluency. We selected the BA and RB, as well as WA and RW as target sites. For each site, we tested both anodal and cathodal stimulation together with the second electrode placed over its contralateral supraorbital region. Based on over- and under-activation patterns of these regions in previous functional imaging studies, we postulated that the normalization of such altered activation could improve speech fluency. Specifically, we hypothesized that the reduction of stuttering severity may be achieved with the following: (i) elevating under-activation in BA, WA, and RW by stimulation with anodal current; and (ii) inhibiting overactivation in RB by stimulation with cathodal

current.

Methods

Participants

Fifteen native Japanese speakers (4 women; aged 19–26 years; median: 24 years) participated in the current study. Inclusion criteria for this experiment were the presence of developmental stuttering and a participant age between 18 and 40 years old. Exclusion criteria were as follows: (i) left-handedness as determined by a FLANDERS handedness questionnaire score between -10 and -5 [29], (ii) any disorder of speech and language other than developmental stuttering, (iii) neurological or psychiatric disorders, (iv) diagnosis of autism spectrum disorder or attention deficit hyperactivity disorder, (v) personal history of seizures and other general exclusion criteria for tDCS as described in a previous study [30].

Eleven of the 15 participants underwent two daily sessions of anodal and cathodal tDCS for BA, RB, WA, and RW. We labeled the session that involved stimulation using the anode over one of the four target sites as the "anodal session." Similarly, the session that involved stimulation using the cathode over one of the four sites was considered the "cathodal session." Four participants underwent either an anodal (n = 2) or cathodal (n = 2) session. According to the FLANDERS handedness questionnaire, one participant was ambidextrous (FLANDERS score: -2) [29]; the rest were right-handed (FLANDERS score > 7). Before the start of the study, the presence of stuttering, based on the Standardized Test for Stuttering, was confirmed by a speech therapist (Y.Y.) [31]. In addition, the speech therapist performed an interview and confirmed (i) the onset of the symptoms in the childhood, (ii) the difficulty in daily life due to the speech dysfluency, and (iii) the absence of declared neurological deficits or other medical

conditions that could explain the speech disturbance. Thus, every participant met the diagnostic criteria of the childhood-onset fluency disorder (stuttering) in the DSM-5 [32] . Among the participants, the severity of stuttering ranged from “very mild” to “moderate” (“very mild,” n = 6; “mild,” n = 3; “moderate,” n = 5; "severe", n = 1). All participants were recruited at a self-help group for PWS (Wisuta kanto, Tokyo). All participants had normal hearing and normal or corrected-to-normal vision. This study was approved by the Ethics Review Committee of the Graduate School of Humanities and Sciences, Tokyo Metropolitan University. All participants provided written informed consent before beginning the study.

Procedure

The anodal and cathodal sessions were separated by at least 24 h. The order of the anodal and cathodal sessions was alternated between participants. One session, which was entirely dedicated to either the anodal or cathodal stimulation for the four target sites, consisted of four blocks of real stimulation and one block of sham stimulation (five blocks in total). We placed 5 min intervals between each block, during which we reset the tDCS montage and checked the impedance of electrodes-to-skin contact for the next block.

For the four real stimulation blocks in a single session, the stimulation site was rotated among the four target sites of BA, WA, RB, and RW (Figure 1a). We generated a total of eight sequences for the order of the real stimulation of these target sites and rotated these patterns among participants. The eight sequences were generated based on the following rules: (i) Determine the stimulation site for the first block among the four target sites (e.g. BA). (ii) Determine the stimulation site for the second block as the one that is the contralateral and non-homologous site with respect to the stimulation site of

the first block (e.g. BA -> RW). (iii) Determine one of the two remaining target sites for stimulation for the third block (e.g. BA -> RW -> WA or RB). (iv) Determine the remaining site as the stimulation site for the forth block (e.g. BA -> RW -> [WA or RB] -> [RB or WA]). These rules were determined in an effort to avoid sequences in which the stimulation site in the block was either ipsilateral or homologous to the stimulation site in the previous block. Ipsilateral or homologous sites are thought to be connected through association and commissural fibers [13,14]; therefore, we hypothesized that some remaining effect of the previous stimulation, if any, might be minimized by maximizing the number of "oblique" transitions (e.g. BA -> RW) among the three transitions. In the sequence of the five blocks in a single session, the order (position) of the sham block was equally distributed from the first to fifth block among the participants. The anodal or cathodal electrode was placed on one of the stimulation sites (BA, WA, RB, or RW) under the condition that no successive blocks had the exactly same stimulation sites. The order of the five blocks was exactly the same between the anodal and cathodal sessions for each participant (Figure 1b).

Stimulation protocol

The study was performed as a double-blind sham-controlled design. tDCS was applied using the DC-STIMULATOR PLUS (neuroConn, Germany) with a pair of surface-soaked sponge electrodes (5 × 7 cm). For the delivery of tDCS, we used a 'study-mode' on the DC-STIMULATOR PLUS to run the stimulation condition (either real or sham stimulation) in a double-blind manner. For the anodal session, the anodal electrode was positioned on one of the four stimulation sites, and the second electrode was positioned on the supraorbital region contralateral to the stimulation side. Similarly, for the cathodal session, the cathodal electrode was positioned on one of the four

stimulation sites, whereas the second electrode was on the contralateral supraorbital region. The positioning of the stimulation electrode was determined using the extended International 10-20 system for EEG electrode placement. The center of the electrode was placed on the point dividing the lines connecting F7 to FC5, F8 to FC6, TP7 to C5, and TP8 to C6 into 1:2, for BA, RB, WA, and RW, respectively (Figure 1).

For the real stimulation blocks, the direct current was ramped up over the initial 10 s, maintained for 190 s at 2 mA and then ramped down to the baseline over 10 s. For the sham stimulation, the current was applied for 30 s at 1 mA at the onset of the block. In order to monitor any serious adverse events during the study, we asked the subjects to rate the sensations (pain, itch, heat, and fatigue) using the 3-scale rating (1:"I have felt", 2: "I might have felt", 3: "I have not felt") at the first and the fifth (last) block of each session. No significant change was found between the two sessions in any of the measures (all $P > 0.1$). All these procedures were consistent with the safety considerations in the application of tDCS [33]. We found no adverse events during or after the tDCS session, including skin burns.

Reading Aloud Task

Five excerpts from Japanese translations of famous fairy tales (e.g., "Ants and the Grasshopper," "Jack and the Beanstalk," and "The Little Prince") were used as the passages in the reading aloud task. The following are the psycholinguistic characteristics of the number of letters (L), the number of clauses (C), and the number of moras (M) of the five passages: Passage 1 (L: 446, C: 116, M: 498), Passage 2 (L: 434, C: 124, M: 561), Passage 3 (L: 491, C: 130, M: 585), Passage 4 (L: 410, C: 101, M: 513), and Passage 5 (L: 421, C: 101, M: 468). All five passages were used for the five blocks in the single session, and the same passage was not repeated within a session.

The same five passages were presented in exactly the same order between the anodal and cathodal sessions for each participant; however, they were presented in a different order between participants.

Each passage was printed on paper and presented on a reading board in front of the participants. As the participants read aloud and their voice was recorded using a microphone (Dynamic Microphone, RadioShack, USA), which was connected to a computer (LIFEBOOK SH54/G, Fujitsu, Japan) with recording software (Audacity 2.1.2, Carnegie Mellon University, USA). Immediately before the recording, participants were asked to silently read through the presented passage to avoid possible speech dysfluency caused by factors other than speech motor, such as temporal difficulties in parsing syntactic structures of sentences. However, we did not have participants read aloud the passages for practice before the experiment.

The participants started reading aloud the presented passage when the experimenter signaled them 20 s after the initiation of the stimulation. The participants were instructed to maintain a natural voice volume and speed, similar to those used in everyday conversation. All participants completed reading the whole passage aloud before the termination of stimulation (range: 66 – 178 sec). The participants were asked to stay still after reading the passage aloud until the experimenter signaled the termination of the block. The tDCS was delivered for a fixed length for all blocks.

Evaluation of speech fluency and statistical analysis

To calculate the stuttering frequency, the number of stuttering events for each recorded sample was counted and divided by the number of morae (Japanese phonological units comparable to syllables in English) in the passage. Based on the Standardized Test for

Stuttering [31], occurrences of stuttering were defined as events that had either (i) repetitions of phonemes, (ii) prolongations of phonemes, or (iii) blocks. The rater (Y.Y.) was blind to the condition of stimulation. To assess intra-rater reliability of the evaluation, the rater re-performed the coding for 25% of randomly selected recorded samples. The second rater (S.T.), who was blind to the stimulation condition, also performed the coding for another 25% of randomly selected samples. The intra-class correlation coefficients for the intra- and inter-rater reliability were 0.98 and 0.90, respectively.

Using the stuttering frequency data from the five blocks of the anodal and cathodal sessions, we first performed a two-way analysis of variance (ANOVA) with the factors of *Block* (i.e., BA, RB, WA, RW, and sham) and *Session* (anodal and cathodal). The analysis turned out to reveal a significant interaction between the two factors. To examine the polarity-dependent effect of tDCS, we separately performed a one-way ANOVA with the *Block* factor for the anodal and cathodal sessions. When performing the parametric tests (ANOVA), we adjusted the degrees of freedom using the Greenhouse-Geisser correction for possible violation of the assumption of sphericity. The statistical significance level was set at $P < 0.05$.

Results

A two-way ANOVA with *Session* and *Block* as factors revealed a significant interaction of *Session* and *Block* ($F(1.96, 19.59) = 5.208$, $P = 0.016$), as well as a main effect of *Session* ($F(1,10) = 6.164$, $P = 0.032$). There was no significant main effect of *Block* ($F(3.00, 30.04) = 1.15$, $P = 0.345$). Because the present number of participants (N=11) did not allow us to perfectly match either the session order (two patterns) or the block

order (eight patterns), we further examined whether the order effects of session (1st and 2nd session) or block (1st to 5th block) had a significant impact on speech fluency. A two-way ANOVA with the factors of *Session Order* and *Block Order* revealed no significant effect of either factor (main effect of *Session Order*: $F(1, 10) = 2.607$, $P = 0.138$, main effect of *Block Order*: $F(4, 40) = 1.226$, $P = 0.315$, *interaction*: $F(4, 40) = 0.437$, $P = 0.781$). We also examined the possibility that the five text passages from the reading aloud task might have influenced speech fluency differently. However, a one-way ANOVA using the factor *Passage* did not reveal a significant effect ($F(4, 40) = 0.94$, $P = 0.451$).

Based on the significant interaction of *Session* and *Block*, we performed follow-up one-way ANOVAs to examine the effect of *Block* separately for the anode and cathodal sessions. We observed a significant main effect of *Block* for the cathodal session ($F(2.089, 20.89) = 3.891$, $P = 0.035$), whereas this effect was not significant for the anodal session ($F(2.516, 25.16) = 2.104$, $P = 0.133$). Post-hoc Dunnett's multiple comparison tests revealed that, compared to the sham block, only the RB block showed a significant difference ($q = 3.001$, $P < 0.05$), whereas the BA ($q = 0.234$), WA ($q = 0.109$), and RB ($q = 0.422$) blocks did not show significant differences.

We had data from four additional participants who underwent either the anodal session only (n=2) or the cathodal session only (n=2); therefore, we repeated a one-way ANOVA with a factor of *Block* separately for the anodal and cathodal sessions using the data from 13 participants (Figure 2). We confirmed a significant main effect of *Block* for the cathodal session ($F(2.82, 33.89) = 4.761$, $P = 0.008$). Post-hoc Dunnett's multiple comparison tests revealed that, compared to the sham block, only the RB block showed a significant difference ($q = 3.652$, $P < 0.05$), whereas the BA ($q = 0.076$), WA ($q =$

0.042), and RW (q = 0.004) blocks did not show significant differences. A main effect of *Block* was also significant for the anodal session (F(2.47, 29.65) = 3.410, P = 0.038). However, post-hoc Dunnett's multiple comparison tests did not reveal significant differences between the sham block and either BA (q = 1.797), RB (q = 0.927), WA (q = 1.805), or RW (q = 1.751).

Discussion

In the present study, we used tDCS to investigate whether modulation of neuronal activity in critical cortical sites for speech production would lead to changes in stuttering frequency in PWS while they read aloud. Among the combinations of stimulation sites and polarities, we observed a highly selective effect of tDCS, such that only the tDCS montage of the cathodal electrode over RB together with the anodal electrode over the left supraorbital region induced a significant reduction in stuttering frequency. We did not observe evidence of a change in stuttering frequency during the anodal session nor the BA, WA, and RW blocks of the cathodal session. These observations suggest that the RB is functionally altered in PWS and that modulation of altered activity by brain stimulation may lead to a reduction in stuttering severity.

The reduction in stuttering severity by a cathode over RB together with an anode over the contralateral supraorbital region may be attributed to the possibility that this tDCS montage had an inhibitory effect on the RB. The RB is likely to be overactive in PWS, therefore, we postulated that this tDCS montage would normalize this overactivation, leading to a reduction in stuttering severity. Indeed, elevated levels of activation in RB and its neighboring motor-related areas is one of the most well-replicated findings in neuroimaging studies of developmental stuttering [5–7]. Our

interpretation is also consistent with the classic hypothesis, which proposes that an altered balance in the neural activity toward the right hemisphere is a cause of stuttering [34]. Therefore, we suggest that our results can be attributed to the possibility that stuttering was reduced by the normalization of the overactivation in the RB by this tDCS montage.

Although overactivation in RB has been replicated in previous studies, several studies suggested that the increased activity of RB may actually reflect better compensation for the defective regions for speech motor control [3,11,12]. According to this hypothesis, rather than causing stuttering, enhanced activity in RB reflects a secondary effect of dysfunctional areas that are truly responsible for stuttering. The basal ganglia and right supplementary motor area (SMA) are candidates for areas that are responsible for causing stuttering, since both are anatomically and functionally connected with RB, driving speech and other motor functions [15,16]. In particular, almost every component of the basal ganglia has shown functional abnormalities related to stuttering, including the caudate nucleus [35], putamen [11], globus pallidus [36], subthalamic nucleus [37], and substantia nigra [38,39]. It has been proposed that the hyperdirect pathway connecting the subthalamic nucleus and RB (inferior frontal gyrus) mediates global response suppression [40]. Therefore, overactivation of this pathway results in increased global inhibition of motor systems, which in turn disrupts control of ongoing and succeeding motor programs for fluent speech [41]. It must also be noted that a recent study revealed altered structural abnormalities in the white matter pathway connecting the right frontal regions with the pre-SMA, as well as with subcortical structures [42]. Therefore, it is possible that reduced stuttering by tDCS involving a cathode over RB in our study might be a consequence of indirect modulation of

dysfunctional activity in the basal ganglia and/or right SMA, which are connected to the RB. Another possible mechanism of improved speech fluency may be that the tDCS on RB modulated working memory processes. Indeed, there has been behavioral evidence suggesting verbal working memory deficits in PWS [43,44]. Because the RB is involved in verbal working memory particularly when memory load is high [45], modulation of the altered working memory system in PWS might influence on speech fluency. Consistent with this possibility, a previous fMRI study reported the RB overactivation in PWS during a verbal working memory task and it was discussed that the verbal working memory task requires executive control processes including inhibition and that impairment in these executive processes might underlie the RB overactivation in PWS [46]. This possibility is consistent with the notion of deficient control processes during speaking that involve the RB, basal ganglia, and/or right SMA.

In contrast to the RB, we did not find evidence for a change in stuttering during the WA or RW block in either the anodal or cathodal session. Given previous consistent neuroimaging findings, which showed reduced activity in the bilateral superior temporal cortex in PWS [9,10], one might predict that normalization of activity by excitatory stimulation might ameliorate stuttering. Although our results did not support this prediction, it is still possible that functional alterations in Wernicke's area contribute to the development of stuttering, because the area is directly connected with frontal speech motor areas through several white matter tracts, including the arcuate fasciculus [13]. A previous neuroimaging study reported that individual anatomical variability in the bilateral planum temporale among PWS is associated with the degree of speech improvement induced by delayed auditory feedback [47]. Similarly, it is possible that the effect of stimulation to WA or RW may vary greatly among PWS, depending on

individual factors, such as anatomical variations. This possibility remains to be clarified with future large scale studies with structural MRI data.

Our observation of improved speech fluency by tDCS may be of interest to researchers and clinicians who seek to apply neuromodulation techniques for a novel treatment of stuttering. However, we note several limitations to our study. First, although a double-blind design was adopted in our study, we used a relatively strong stimulation intensity (i.e. 2 mA), and it is unknown whether the participants felt or did not feel any difference in evoked sensations between the real stimulation and sham stimulation blocks. We need additional data to confirm whether participants were able to discern between the active and sham stimulation using the same tDCS montage as in the present study. However, we noted that stuttering severity was reduced in a highly selective manner such that only the RB block in the cathodal session had a significant effect. Given this selectivity, the reduction in stuttering for the cathode RB block is unlikely to be explained by the expectation effect or other factors that are related to possible violations from strict double-blind procedures. Second, one may raise a concern that the inter-block interval of 5 min might not be long enough to eliminate the after-effects of the stimulation of the previous block. We adopted the relatively short inter-block interval to reduce the total experimental time and to keep the concentration and motivation of the participants throughout the experiment. In addition, the previous tDCS studies examining the duration of after-effects based on the motor evoked potential (MEP) showed that the change of MEP returned to the baseline level within 5 min after the 5 min cathodal stimulation [17], [48]. Because the duration of the tDCS block was 190 sec in our study, we expected that the after-effects were effectively eliminated within the inter-block interval of 5 min. If there were some remaining

after-effects, one might expect that such effects would accumulate over the stimulation blocks. However, we observed no significant effect of block order, indicating that accumulative after-effects were negligible. The third and most significant limitation of our study for clinical application is that we examined changes in speech fluency only when stimulation was being applied; thus, the duration of the stimulation effect is currently unknown. A previous tDCS study of stuttering has shown that the speech improvement induced by 1 mA of anodal tDCS over the left inferior frontal cortex was maintained up to 6 weeks after the intervention [28]. Although we did not observe significant speech improvement for the BA block in the anodal session, it is possible that the effect of tDCS is different between online and offline periods given several neuromodulatory factors induced by stimulation with various time scales [49]. We also note that, in our study as well, the effect of anodal BA stimulation was improving, rather than worsening, speech fluency. Since the present study showed that the RB block in the cathodal session significantly improved speech fluency, it would be interesting to examine its offline effect in a future study. Further studies will be needed to develop the optimal tDCS protocol for improving speech fluency over a significant duration of time by tailoring stimulation parameters, such as the stimulation intensity, stimulation duration, and electrode placement, for each individual.

In conclusion, the present tDCS study demonstrated that speech fluency was significantly improved by the tDCS montage of a cathodal electrode over RB and an anodal electrode over the left supraorbital region in PWS. This result suggests that speech fluency in PWS may be improved either by directly normalizing overactivation in RB or by indirectly modulating activity in speech motor control areas that are connected with the RB. Further progress may be made toward its clinical application by

incorporating individual differences in brain organization and by retaining the stimulation effects over an extended period of time.

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Authors Contributions. Conceived and designed the experiment: Y.Y., R.H., Performed experiment: Y.Y., R.H., Analyzed speech data: Y.Y., S.T., Performed statistical analysis: Y.Y., R.H., Wrote the paper: Y.Y., R.H.

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Figure legends

Figure 1. (A) Transcranial direct current stimulation (tDCS) montages for anodal and cathodal sessions. The position of the center of the first electrode for each stimulation site (either BA, RB, WA, or RW) was determined based on the extended International 10-20 system for the electroencephalography (EEG) electrode system (denoted in circles; see Methods/Stimulation Protocols). Red and blue electrodes denote anode and cathode electrodes, respectively. The second electrode was placed over the supraorbital region contralateral to the first electrode. (B) Illustration of sequences of stimulation blocks in anodal and cathodal sessions in individual subjects. “A” and “C” in "Session" denote the anodal and cathodal sessions, respectively. Rectangles in red or blue straight lines denote the real anodal or cathodal stimulation blocks. Rectangles in dotted black lines denote the sham stimulation block. Notations in rectangles denote the target stimulation sites. The order of the real stimulation of the four target sites was determined based on the rule described in the Methods section (Procedure). The order (position) of the sham block was evenly distributed from the first to the fifth block. Note that the order of the five blocks was exactly the same between the anodal and cathodal sessions in each individual. Note also that the order of the anodal and cathodal sessions was alternated between participants. BA, Broca’s area; RB, right homologue of Broca’s area; WA, Wernicke’s area; RW, right homologue of Wernicke’s area.

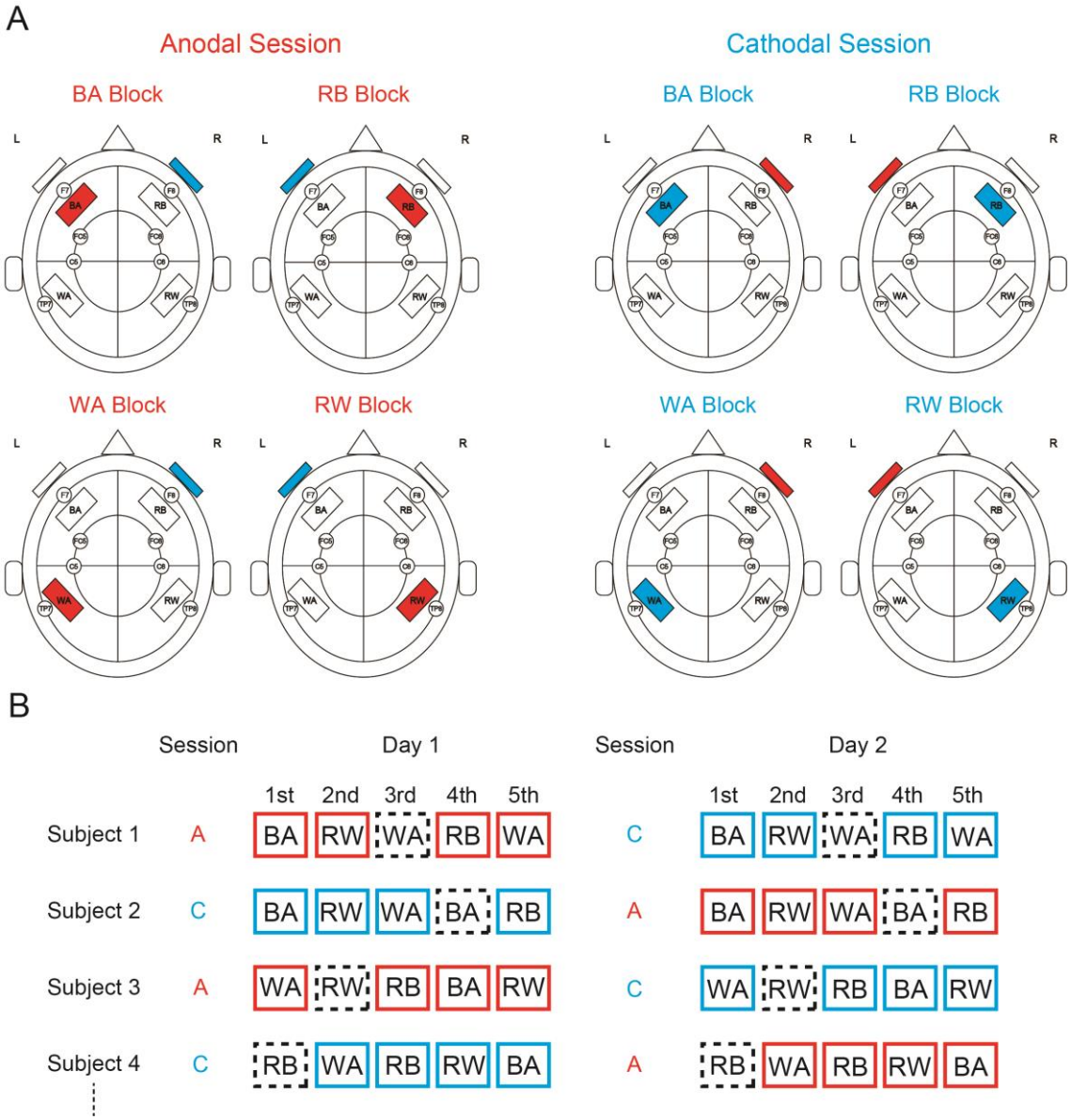

Figure 2. Percentage of stuttered moras (%sm) during the BA, RB, WA, RW, and sham blocks in the anodal (A) and cathodal (B) sessions (N=13 each). Bar graphs denote the mean %sm and error bars denote the standard error of mean (SEM). Asterisks denote a significant difference from the sham block as revealed in the post-hoc test ($P < 0.05$). BA, Broca's area; RB, right homologue of the Broca's area; WA, Wernicke's area; RW, right homologue of Wernicke's area.