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Modulating transcallosal and intra-hemispheric brain connectivity with tDCS: Implications for interventions in Aphasia

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Abstract.
Background/Objective: Transcranial direct current stimulation (tDCS) can enhance or diminish cortical excitability levels depending on the polarity of the stimulation. One application of non-invasive brain-stimulation has been to modulate a possible inter-hemispheric disinhibition after a stroke. This disinhibition model has been developed mainly for the upper extremity motor system, but it is not known whether the language/speech-motor system shows a similar inter-hemispheric interaction. We aimed to examine physiological evidence of inter- and intra-hemispheric connectivity changes induced by tDCS of the right inferior frontal gyrus (IFG) using arterial-spin labeling (ASL) MRI.
Methods: Using an MR-compatible DC-Stimulator, we applied anodal stimulation to the right IFG region of nine healthy adults while undergoing non-invasive cerebral blood flow imaging with arterial-spin labeling (ASL) before, during, and after the stimulation. All ASL images were then normalized and timecourses were extracted in regions of interest (ROIs), which were the left and right IFG regions, and the right supramarginal gyrus (SMG) in the inferior parietal lobule. Two additional ROIs (the right occipital lobe and the left fronto-orbital region) were taken as control regions.
Results: Using regional correlation coefficients as a surrogate marker of connectivity, we could show that inter-hemispheric connectivity (right IFG with left IFG) decreased significantly ($p < 0.05$; r-scores from 0.67 to 0.53) between baseline and post-stimulation, while the intra-hemispheric connectivity (right IFG with right SMG) increased significantly ($p < 0.05$; r-scores from 0.74 to 0.81). A 2×2 ANOVA found a significant main effect of HEMISPHERE ($F(8) = 6.83$, $p < 0.01$) and a significant HEMISPHERE-by-TIME interaction ($F(8) = 4.24$, $p < 0.05$) in connectivity changes. The correlation scores did not change significantly in the control region pairs (right IFG with right occipital and right IFG with left fronto-orbital) over time.
Conclusion: Using an MR-compatible DC stimulator we showed that ASL-MRI can detect tDCS-induced modulation of brain connectivity within and between hemispheres. These findings might affect trial designs focusing on modulating the non-dominant hemisphere to enhance language/speech-motor functions.

Keywords: Resting state fcMRI, arterial spin labeling, tDCS, transcallosal connectivity, aphasia, rehabilitation, brain stimulation, plasticity

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1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can modulate resting membrane potential and spontaneous neuronal discharge rates, and through those mechanisms can change cortical excitability; anodal stimulation has been associated with an increase in cortical excitability and cathodal stimulation has been associated with a decrease in cortical excitability of a targeted brain region, with effects that outlast the stimulation period (Nitsche & Paulus, 2000; Priori, et al., 1998; Schlaug & Renga, 2008). TDCS has been used widely in stroke recovery studies, mostly in patients with motor impairments and lesions involving the descending motor system. Here, tDCS has been used to aid stroke recovery by upregulating the excitability in intact portions of the ipsilesional hemisphere and down-regulating excitability in the contralesional hemisphere (Bolognini et al., 2011; F. Hummel et al., 2005; F. C. Hummel & Cohen, 2006; Khedr et al., 2013; Schlaug & Renga, 2008; Schlaug, Renga, & Nair, 2008) under the assumption that uninhibited contralesional activity might interfere with the stroke recovery process. When non-invasive brain-stimulation is used concurrently with rehabilitation therapy in patients, it can enhance recovery when compared to just the behavioral therapy by itself (Hamilton, Chrysikou, & Coslett, 2011; Lindenberg, et al., 2010; Page, Cunningham, Plow, & Blazak, 2015).

Although the application of brain stimulation to the lesional and non-lesional hemisphere and its interference in the disinhibition model has been developed mainly for the hand-motor system, various stimulation montages and types of interventions have been applied to regions involved in the language/speech-motor system and results have varied (Schlaug, Marchina, & Wan, 2011). Some findings from the use of tDCS and transcranial magnetic stimulation (TMS), in particular those studies that have blocked the contralesional inferior frontal gyrus (typically the right IFG) to treat chronic aphasia, have largely been interpreted as supporting the model of inter-hemispheric inhibition (Fregni & Pascual-Leone, 2007). However, there have also been conflicting studies that reported improved language/speech-motor performance measures in patients with aphasia after undergoing cathodal (Monti et al., 2008), anodal (Baker, Rorden, & Fridriksson, 2010) stimulation of the ipsilesional frontal region, anodal stimulation of the contralesional frontal region (Vines, Norton, & Schlaug, 2011), and bihemispheric stimulation montages (Manenti et al., 2015; Marangolo et al., 2014; Marangolo et al., 2016). Most interventions with non-invasive brain stimulation have employed inhibitory stimulation of contralesional hemisphere structures, which may in turn facilitate increased recruitment of perilesional regions on the lesional hemisphere (Hamilton et al., 2011). Yet, a recent study (Shah-Basak et al., 2015) showed that both cathodal stimulation of the lesional hemisphere and anodal stimulation of the unaffected hemisphere could have beneficial effects.

For most adults, speech-motor functions show a left-hemisphere dominance and the left inferior frontal gyrus (IFG), also known as Broca's area, plays a critical role in the mapping of sounds to actions and the sequencing of these motor actions into meaningful units (Binkofski et al., 2000; Binkofski & Buccino, 2004; Blank, Bird, Turkheimer, & Wise, 2003; Lahav, Saltzman, & Schlaug, 2007). Others have also attributed roles in music and language syntax processing to this region (Koelsch, et al., 2005; Musso et al., 2015). Local injury to this region and its surrounding regions, such as from a stroke, can lead to a type of aphasia that is characterized by a decrease in speech fluency, impairments of repetition and naming, and in general, an agrammatic speech (Alexander & Hillis, 2008). In the aphasia recovery process, the transcallosal connections between the lesioned left IFG and its connections to the right IFG homotop might play an important role. It has been argued that connections through the corpus callosum (CC) are predominantly inhibitory suggesting that homotop regions, particularly if they are of similar size, might be mainly inhibiting each other through transcallosal fibers (Bloom & Hynd, 2005; Meyer, et al., 1995; Rosen, Sherman, & Galaburda, 1989). In the case of a focal lesion in one hemisphere, the contralesional region may become disinhibited and in turn exert unopposed inhibition (from the non-lesional hemisphere) back onto the lesional hemisphere. This has been used to support the use of inhibitory stimulation applied to right inferior frontal regions to facilitate speech-motor and language recovery (Martin et al., 2004; Murase, Duque, Mazzocchio, & Cohen, 2004; Perez & Cohen, 2009; Saur et al., 2006; Thiel et al., 2006). Evidence for right hemisphere interference with recovery has been provided via TMS studies for the "hand-motor" system, but is lacking or cannot be obtained via TMS for the "speech-motor" system. For example, Martin and colleagues (Martin et al., 2004) showed that

inhibitory repetitive TMS of the right Broca's homotop in patients with non-fluent aphasia increased naming ability, suggesting an inhibitory effect of the right IFG on the left which is presumably reduced via applying inhibitory stimulation to the right IFG. However, a recent study by Shah-Basak et al. (Shah-Basak et al., 2015) also found excitatory stimulation benefits (using anodal tDCS) if the stimulation is applied over F4 of the right hemisphere (using the 10–20 system for localizing the scalp target position of stimulation). This is in agreement with earlier work by our group showing an enhanced effect of Melodic Intonation Therapy when it is coupled with anodal tDCS over the right posterior IFG on measures of speech fluency (Vines et al., 2011). Thus, the interaction between right and left hemisphere, particularly with regard to speech-motor regions, might be more complex than previously thought. There are certainly conflicting data that the right hemisphere can not only hinder recovery of the left, but might also have positive effects on recovery, particularly in nonfluent aphasic patients with large left hemisphere lesions, by modifying behaviorally relevant connections between right hemisphere vocal perception and vocal action regions (Schlaug et al., 2011; Wan, et al., 2014).

Neuroimaging techniques, such as blood oxygen level dependent contrast (BOLD) as well as arterial spin labeling (ASL) blood flow imaging can be used to non-invasively measure markers of brain activity. Previous studies have shown that changes in local excitability induced and/or modulated by non-invasive brain-stimulation can be captured by either BOLD or ASL. These MR techniques have the advantage of not just detecting neuronal activity in locations targeted by the non-invasive stimulation, but also in remote, connected regions of the brain. There are studies which have looked at BOLD MR signal changes in conjunction with TMS and tDCS (Baudewig et al., 2001; Kwon et al., 2008; Zheng, Alsop, & Schlaug, 2011), as well as PET signal changes (Lang et al., 2005). These studies demonstrated the safety of performing noninvasive brain stimulation in the MR environment and the validity of using MR correlates of brain activities to investigate the effect of brain stimulation on local excitability levels, but have also pointed out problems that BOLD-fMRI might pose on measuring the effects of electrical stimulation (Antal et al., 2014). Our previous study (Zheng et al., 2011) has shown the safety and efficacy of using ASL in conjunction with tDCS. ASL is a noninvasive imaging technique that magnetically tags arterial blood water as an endogenous tracer (Alsop & Detre, 1998; Detre, Leigh, Williams, & Koretsky, 1992). Its excellent temporal stability (Aguirre, Detre, Zarahn, & Alsop, 2002), as compared to possible signal drifts in MR-BOLD imaging, is particular useful for examining tDCS effects, which is typically applied for several minutes and has effects lasting far beyond the cessation of stimulation (Nitsche, Liebetanz, Tergau, & Paulus, 2002; Nitsche & Paulus, 2000).

In additional to looking at brain activity or blood flow changes over time, relational information can be examined with the use of functional connectivity, which is a neuroimaging approach that relates brain activity over time in one region with the activity in another region (Dai, Varma, Scheidegger, & Alsop, 2016; Fox & Greicius, 2010; Friston, 1994; Sporns, Tononi, & Edelman, 2000). Although the basic concept of functional connectivity assumes that two or more regions belong to the same functional network if their neural timecourses are correlated with each other, there are currently multiple approaches for assessing the clinical utility of rs-fMRI in stroke patients and in patients with focal lesions in general (Grefkes & Fink, 2014). Disrupted resting state networks have been shown to reflect functional impairment in stroke patients (Carter et al., 2010; Park et al., 2011). Recovery of functional deficits is associated with an increase in connectivity in components of a resting state network (Golestani, Tymchuk, Demchuk, Goodyear, & Group, 2013; Wang et al., 2010). Furthermore, it has been shown that focal tDCS can disrupt resting state networks, for example the dorsolateral prefrontal network (Keeser et al., 2011; Stagg et al., 2013) or the motor network (Amadi, Ilie, Johansen-Berg, & Stagg, 2013). Non-invasive stimulation like TMS and tDCS allows causality to be inferred between the stimulation and the measured changes in functional connectivity, as it is an extrinsic perturbation of the resting network (Eldaief, Halko, Buckner, & Pascual-Leone, 2011) as well as between the stimulated regions and any behavior that draws on that region (Mathys, Loui, Zheng, & Schlaug, 2010; Vines, Schnider, & Schlaug, 2006).

Thus, in this study we aimed to examine the hypothesis that tDCS applied to the right IFG modulates interhemispheric (transcallosal IFG to IFG) as well as intrahemispheric (ipsihemispheric IFG to SMG) functional connectivity using ASL-rsfMRI.

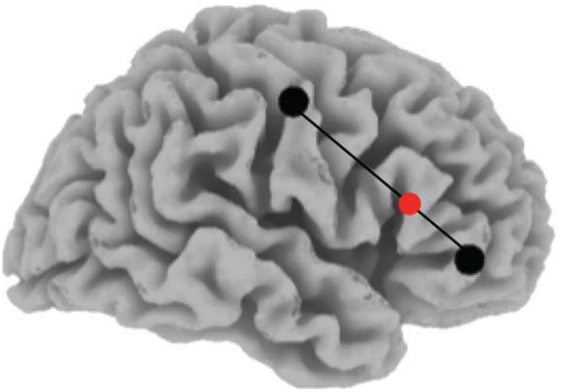

Fig. 1. Targeting of the right posterior IFG using the 10-20 EEG system. The right IFG was identified as 1/3 of the distance between F8 and C6.

2. Material and methods

2.1. Subjects

Nine healthy, young adults participated in this study (mean age 31.2; SD 6.2; 5 males; all right-handed). All subjects gave their written informed consent following protocol approval by the Committee on Clinical Investigations at our institution.

2.2. TDCS setup

The tDCS was delivered by an MRI-compatible battery-driven constant-current stimulator (Eldith DC-Stimulator) through a pair of MRI-compatible electrodes (NeuroConn, Germany), with a rectangular surface area of 20 cm^2. All subjects were given anodal tDCS at a strength of 1 mA for 10 minutes, with the anodal electrode placed over the right IFG (1/3 of the distance between F8 and C6 on the standard 10-20 EEG system; see Fig. 1) and the cathodal electrode over the left supra-orbital region.

2.3. MR image acquisition

After the electrodes were positioned and held securely by elastic bandages, subjects were positioned in a 3-Tesla General Electric MR scanner and images were acquired using body coil transmission and a standard 8-channel radio-frequency receive-only head coil. Head motion was minimized by using foam padding and forehead restraining straps.

A scout image was first acquired to grossly assess the head positioning in the scanner, followed by a high-resolution strongly T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (voxel size $0.93 \times 0.93 \times 1.5$ mm). This was then followed by a series of ASL acquisitions, where the stimulation was in an off state for the first 15 scans (approximately 8 minutes), then the tDCS device was turned on for the next 19 scans (approximately 10 minutes), and off again for the final 15 scans (approximately 8 minutes). Subjects kept their eyes closed during all the ASL acquisitions. Pseudo-continuous arterial spin labeling was used due to its high efficiency and increased signal-to-noise ratio (Dai, Garcia, de Bazelaire, & Alsop, 2008). ASL perfusion images were acquired with a 3D stack of spirals Rapid Acquisition with Refocused Echoes (RARE) imaging sequence with 40 slices of 4 mm thickness. Each acquisition was performed with three spiral interleaves and alternation between label and control images, producing an in-plane resolution of 3.64 mm. The repetition time (TR) of each ASL acquisition was 5 s. For each of the three spiral interleaves, control and label images were acquired consecutively, and therefore each 3-D ASL image acquisition required 6 TRs (totaling 30 s). Forty-nine 3D-ASL images were collected in approximately 26 minutes. Diffusion tensor imaging (DTI) was acquired using a single-shot, spin-echo, echo-planar imaging sequence (TE = 86.9 ms, TR = 10,000 ms, FOV = 240 mm, slice thickness = 2.5 mm, resolution: $2.5 \times 2.5 \times 2.5$ mm, no skip, NEX = 1, axial acquisition, 30 non-collinear directions with *b*-value = 1000 s/mm, 6 images with *b*-value = 0 s/mm). DTI was used for tractography to determine the connectivity of our inter- and intra-hemispheric regions.

2.4. ASL processing and analysis

All image processing steps were done using FSL (v4.1.4, http://fsl.fmrib.ox.ac.uk/fsl). The ASL images were first coregistered to their corresponding T1-weighted anatomical image. The anatomical images were then registered to FSL's 2 mm T1 template using linear algorithms (FLIRT) and then the transformation matrix was applied to the ASL images to normalize all ASL images to the template space.

We used the Harvard-Oxford atlas to identify our regions of interest (ROIs). Our ROIs were chosen as the left and right IFG regions (BA44 + BA45), as well as the right supramarginal gyrus (SMG; BA 40) region (see Fig. 2). The right IFG was targeted by tDCS and the left IFG served as an example to test

how activity could be modulated across the corpus callosum. The right SMG region has been shown to be connected to the right IFG and served as an example to test how activity could be modulated within one hemisphere between regions that are structurally connected, but separated by several inches. Two additional control regions were taken – the right occipital lobe (as an example of a region that might not be related to the right IFG and might represent unrelated intra-hemispheric connectivity) and the left fronto-orbital region (as an example of a region that might not be related to the right IFG and might represent unrelated inter-hemispheric connectivity). The left fronto-orbital region was also the location of the reference electrode, which allowed us to also control for electrode effects. Each ROI was used to extract the blood flow measures from the ASL images. Each subject's blood flow time course was then normalized by its average time course (x-avg/avg) for each ROI.

The timecourse of MR signal changes of the ROI underneath the stimulating electrode (right IFG) was split into baseline, stimulation, and post-stimulation phases. We examined overall blood flow changes between the phases by looking at the changes in average blood flow of each phase.

In addition, we compared the functional connectivity of regions by looking at the correlations between right and left IFG as an example of transcallosal connectivity and the right IFG and right SMG as an example of intrahemispheric connectivity. The connectivity profiles between the right IFG and right occipital region as well as the right IFG and left fronto-orbital region were taken as control connectivity pairs. The scans right at the boundary of the baseline/stimulation periods as well as at the stimulation/post-stimulation periods were removed. As a result, the first 14 scans were taken as the baseline condition and the final 14 scans as the post-stimulation condition. We compared the changes in correlations, our measurement for connectivity, between inter- and intra-hemispheric regions between the conditions and with the correlations between the right IFG and our control region pairs.

Two separate analyses were conducted to investigate this change in connectivity. The first analysis concatenated all the scans for each condition and inter-hemispheric (IFG-IFG), intra-hemispheric (IFG-SMG), and control correlations (IFG-frontoorbital and IFG-occipital) were then conducted. Thus, we used correlation coefficient between two regions as a surrogate marker of connectivity. These correlation coefficients were then compared between baseline and post-stimulation to determine changes in connectivity. The second analysis calculated r-scores for the same inter-hemispheric (IFG-IFG) and intra-hemispheric (IFG-SMG) connections per subject. The r-scores were then converted to z-scores and used as the dependent variable in a 2×2 ANOVA design matrix, with hemisphere (inter-hemispheric vs intra-hemispheric) and time (baseline vs post-stimulation) as the two factors. The same analyses were also conducted in the control region pairs as a comparison.

2.5. DTI processing and tractography

Diffusion tensor imaging and tractography was performed to show that left and right IFG are connected through the corpus callosum and that the right IFG is structurally connected with the right SMG. The diffusion data were processed using FSL (4.1.4). Preprocessing steps included correction for eddy current effects, skull stripping, head motion correction with affine multiscale two-dimensional registration, as well as estimation and fitting of a diffusion tensor model at each voxel using DTIFIT to calculate the lambda values for each principle eigenvector and FA. The FA images were normalized to the FMRIB standard FA template using linear and nonlinear algorithms (FLIRT and FNIRT). BEDPOSTX was conducted on these images in preparation for tractography.

The ROIs for tractography were the same IFG and SMG regions from the Harvard-Oxford atlas, but these regions were first masked with the FA template at FA > 0.25 to only include the white matter underlying the IFG and SMG cortex. The right IFG was used as the seed region and the left IFG (for inter-hemispheric connections) as well as the right SMG (for intra-hemispheric connections) as target regions. All tractography was conducted in normalized space using the registration parameters from the FA normalization. Each subject's tracts were then thresholded at its 50th percentile, binarized and summed together. The group tracts were then thresholded again, such that at least 5 subjects had to have a tract at that voxel location.

3. Results

The DTI analysis revealed that indeed the right IFG connects with the left IFG via transcallosal fibers and the right IFG also connects with the right SMG via the

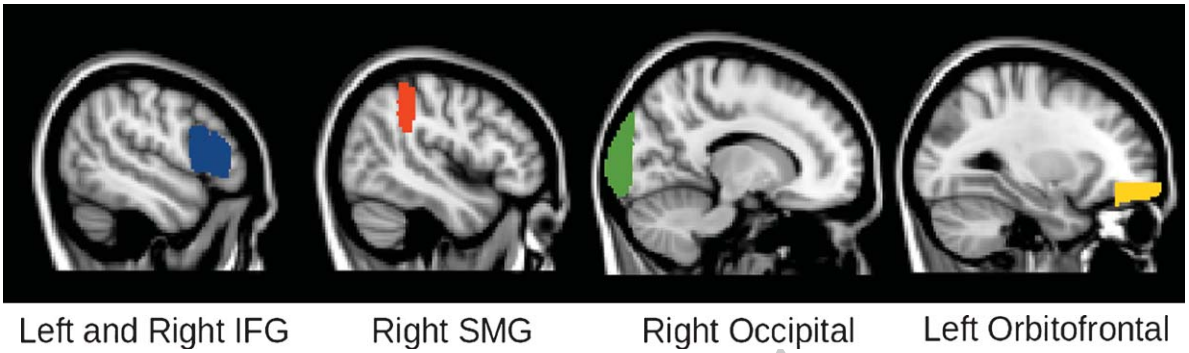

Fig. 2. The left and right IFG (Blue), right SMG (Red), right occipital (Green), and left orbitofrontal (Yellow) ROIs used to extract blood flow values are shown overlaid on T1-weighted images.

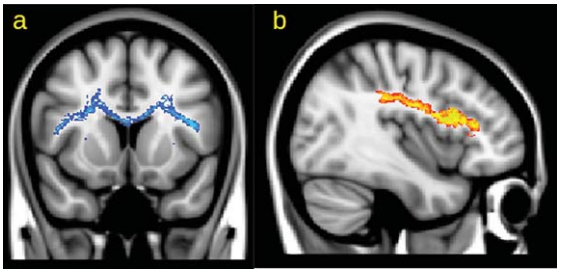

Fig. 3. Tractography showing a) transcallosal IFG-IFG fibers and b) the Arcuate Fasciculus fibers connecting right IFG with right SMG ROIs.

arcuate fasciculus (see Fig. 3). This structural connectivity allowed us to examine inter-hemispheric and intra-hemispheric functional connectivity of tDCS induced modulation of cortical activity in the tDCS-targeted right IFG.

The targeted right IFG did not show a significant change in the averaged blood flow between baseline and stimulation phases ($p < 0.8$). However, there was a 2% ($p < 0.05$) increase in average blood flow between the baseline and post-stimulation phases. The signal intensities between the baseline and post-stimulation phases in the left, unstimulated IFG, left fronto-orbital, right SMG, and right occipital regions did not show any significant differences (all $p > 0.1$) (see Fig. 4).

In using correlation coefficients between two regions as a surrogate marker of functional connectivity, we found the baseline inter-hemisp heric connectivity between both IFGs to be lower than the intra-hemispheric connectivity between the right IFG and SMG. The inter-hemispheric (IFG-IFG) connectivity decreased significantly ($p < 0.05$) between baseline and post-stimulation (r-scores decreased from a baseline-level of 0.665 to a post-stimulation level of 0.534 post-stimulation). At the same time, the intra-hemispheric (IFG-SMG) connectivity increased significantly ($p < 0.05$) between baseline and post-stimulation (r-scores from 0.736 to 0.807). Connectivity between the right IFG and the two control regions (right occipital and left frontoorbital) did not change significantly over time ($p > 0.1$). From the 2×2 ANOVA design, we found a significant main effect of HEMISPHERE ($F(8) = 6.83$, $p < 0.01$) and a significant HEMISPHERE-by-TIME interaction ($F(8) = 4.24$, $p < 0.05$) in connectivity changes (see Fig. 5). The same analyses in the control region pairs did not yield significant correlation changes ($p > 0.2$) nor interaction effects ($p > 0.2$).

4. Discussion

Our results show that non-invasive brain stimulation with tDCS and simultaneous non-invasive blood flow imaging with ASL in the MRI environment is technically feasible and safe. The stimulation

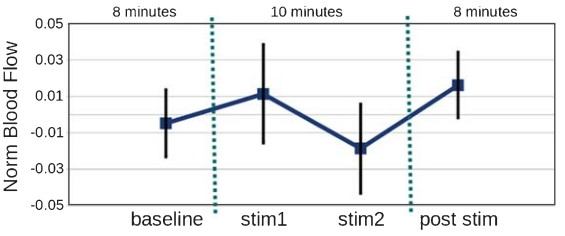

Fig. 4. Averaged time course (with standard error bars) of blood flow measures extracted from the right IFG (the stimulated region) per condition, showing insignificant change during the stimulation phase and a slight but significant increases in blood flow (+2%) after cessation of stimulation. The stimulation condition was split into two halves.

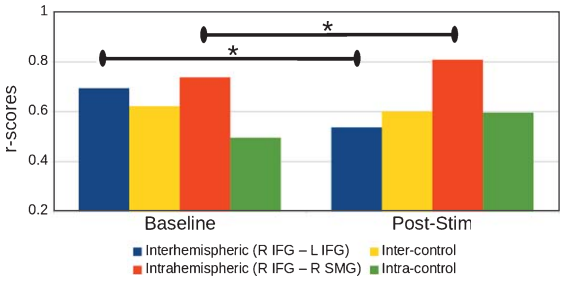

Fig. 5. Concatenated inter-hemispheric and intra-hemispheric connectivity changes between baseline and post-stimulation phases of functionally connected region pairs and control region pairs. The IFG-IFG (inter-hemispheric) showed a significant decrease in connectivity, the IFG-SMG (intra-hemispheric) showed a significant increase in connectivity, while the inter- and intra-hemispheric control pairs did not reveal any change that was statistically significant.

modulated the rCBF quickly and reproducibly in the targeted brain region underneath the electrode, however the time course was different from what we previously reported (Zheng et al., 2011), possibly because a different brain region was target (right IFG in this study and precentral gyrus region in Zheng et al., 2011 (Zheng et al., 2011)). The regional blood flow did not change between baseline and stimulation phases, but the post-stimulation phase still showed a small (2%) but significant increase when compared to baseline. This difference in the magnitude of change may be due to either a different stimulation device (NeuroConn (current study) vs Phoresor (Zheng et al., 2011)) or a lower stimulation strength (1.0 mA in current study vs 1.5 mA in Zheng et al., 2011 (Zheng et al., 2011)) being used. However, the consistent increase in post-stimulation blood flow still supports the use of regional blood flow imaging with ASL as a good surrogate marker of local tDCS effects and that imaging can be used to measure cerebral correlates during and after the stimulation, as after-effects of tDCS have been shown to persist for up to 90 min after sessions of 1 mA polarization lasting 9–13 minutes (Nitsche, 2002; Nitsche et al., 2003).

The anatomical connectivity between right and left IFG has been well established and we have provided even more evidence that both IFGs are structurally connected via transcallosal fibers. Furthermore, we also provided evidence that the right IFG connects to the right SMG (inferior parietal lobule) via the arcuate fasciculus. This structural connectivity formed the basis for us to examine potential differences of anodal stimulation on inter- and intra-hemispheric connectivity. We found the baseline inter-hemispheric connectivity between homotop regions to be lower than the intra-hemispheric connectivity between regions known to be connected via the arcuate fasciculus. If indeed the predominant mode of action through the corpus callosum is inhibitory, then increasing local excitatory activity in the right IFG might result in increased inhibition of the left IFG which might be reflected in decreased functional connectivity or a decrease in coupling between those two homotop regions. At the same time, we saw an increase in functional connectivity between IFG and SMG on the right side. These modulations of intrinsic activity might explain some of the findings in aphasic recovery studies. Vines et al (Vines et al., 2011) and also recently Shah-Basak et al. (Shah-Basak et al., 2015) have used anodal stimulation over the right IFG. Beneficial effects were seen in both of these studies, although there are also findings to the contrary by other studies showing behavioral effects after cathodaltDCS or inhibitory TMS of the same regions (Hamilton et al., 2010; Martin et al., 2009; Naeser et al., 2010; Schlaug et al., 2011; Weiduschat et al., 2011). Floel and colleagues (Floel et al., 2011) and also recently Costa and colleagues (Costa, et al., 2015) stimulated the right inferior parietal operculum (presumable the right SMG) and found that this has an effect on naming suggesting that stimulating different nodal points of a right hemisphere functional network (connected via the Arcuate Fasciculus) might have beneficial effects in recovery of language/speech-motor functions. These contradictory anodal versus cathodal findings after stimulating the right IFG are somewhat difficult to explain and put into context with our current study. Although it appears that anodal stimulation to the right IFG will lead to less transcallosal and more intra-hemispheric connectivity, it is also possible that cathodal stimulation to the right IFG would lead to less transcallosal interaction as well and would increase interaction of left hemispheric language/speech-motor regions (with reduced interference from the right), obviously an approach that would only work if sufficient language/speech motor regions remain intact on the left hemisphere after a stroke.

After anodal stimulation, there was a decrease in inter-hemispheric connectivity in conjunction with an increase in intra-hemispheric connectivity, indicating the strengthening of this effect. This is different than what has been described in a recent study (Amadi et al., 2013) that found increased inter-hemispheric coherence of resting fMRI signal between left and

right supplementary motor area and hand areas of M1 after cathodal stimulation of the motor region, while no significant changes in resting state connectivity was seen after anodal or sham stimulation. Other studies have found modulation of neural networks with tDCS (Amadi et al., 2013; Clemens et al., 2014; Fox et al., 2014; Hunter et al., 2015; Keeser et al., 2011; Krishnamurthy, Gopinath, Brown, & Hampstead, 2015; Park et al., 2013; Pena-Gomez et al., 2012; Weber, Messing, Rao, Detre, & Thompson-Schill, 2014), but none of these studies has specifically examined the differential modulatory effects of interhemispheric and intrahemispheric connectivity when anodal tDCS is applied to the right IFG.

As a note of interest, functional connectivity within an intrinsic network is often thought of as being static, where the default network remains relatively constant across scanning sessions (Chang & Glover, 2010). These static assumptions have affected how resting state networks are analyzed, specifically by computing region-to-region functional connectivity across an entire scanning session, with the assumption that the strength of these couplings do not change appreciably over time. By showing that these couplings can be modulated predictably by external sources, such as tDCS, we may have to alter how these analyses are modeled.

Functional connectivity changes due to effects of stimulation may have multiple biophysical determinants, such as the existence of bidirectional connections (excitatory or inhibitory), path length, density, and presence of intermediate nodes (Achard, et al., 2006; Bullmore & Sporns, 2009) that may result in observations that are dependent on the stimulated region.It has also been proposed that these changes in connectivity can be a result of changes in signal to noise ratio (Polania, Paulus, & Nitsche, 2012). Since anodal stimulation modulates brain activity by increasing the potential for action potentials (Antal et al., 2004), the increased spontaneous neuronal discharge rates will increase the background activation in the stimulated region and possibly in connected areas and thus decrease the signal to noise ratio and change synchronization with related regions. The interregional synchronization change may differ from region to region depending on whether or not the predominant functional connection between regions is inhibitory or excitatory.

Our study has several limitations. First, we cannot conclude that the correlation changes of the distal ipsilateral and contralateral brain regions with the stimulated IFG region are causal since correlations are non-directional and it is theoretically possible that correlations could change over time. Second, our design would have benefited from having a cathodal condition to determine whether or not inter- and intra-hemispheric connectivity can be modulated differently depending on the polarity of the direct current. Third, the limited number of subjects used in this study makes it difficult to generalize our findings, however, our results can serve as hypothesis-generating for future studies.

5. Conclusion

TDCS and resting state ASL-MRI can be used to assess the effects of modulating intrinsic brain activity, not only directly under the electrode, but also in remote, but connected regions of the brain. Understanding the modulation of intrinsic connectivity might not only offer new interventions for regions of the brain that might be remote from the stimulation site, but it might offer us insights into how non-invasive brain-stimulation might exert its effect and modulate network interactions. TDCS and resting state ASL-MRI may further our insights into a variety of interesting clinical neuroscience questions and move us closer to the goal of a reliable, non-invasive method for controlled modulation of brain activity.

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