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Sex differences in effects of tDCS and language treatments on brain functional connectivity in primary progressive aphasia

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ABSTRACT

Primary Progressive Aphasia (PPA) is a neurodegenerative disorder primarily affecting language functions. Neuromodulatory techniques (e.g., transcranial direct current stimulation, active-tDCS) and behavioral (speech-language) therapy have shown promising results in treating speech and language deficits in PPA patients. One mechanism of active-tDCS efficacy is through modulation of network functional connectivity (FC). It remains unknown how biological sex influences FC and active-tDCS or language treatment(s). In the current study, we compared sex differences, induced by active-tDCS and language therapy alone, in the default mode and language networks, acquired during resting-state fMRI in 36 PPA patients. Using a novel statistical method, the covariate-assisted-principal-regression (CAPs) technique, we found sex and age differences in FC changes following active-tDCS. In the default mode network (DMN): (1) men (in both conditions) showed greater FC in DMN than women. (2) men who received active-tDCS showed greater FC in the DMN than men who received language-treatment only. In the language network: (1) women who received active-tDCS showed significantly greater FC across the language network than women who received sham-tDCS. As age increases, regardless of sex and treatment condition, FC in language regions decreases. The current findings suggest active-tDCS treatment in PPA alters network-specific FC in a sex-dependent manner.

1. Introduction

Language deficits are the primary manifestations in several early-onset neurodegenerative syndromes. These deficits affect the personal, social, and economic lives of an increasing percentage of working adults, typically during their 5th and 6th decades of life. These syndromes have been coined as primary progressive aphasia (PPA) (Mesulam, 1982). Language impairments occur in common neurodegenerative pathologies including Alzheimer's disease (AD), in the logopenic variant of primary progressive aphasia (lvPPA), and fronto-temporal dementia (FTD) in the non-fluent/agrammatic PPA (nfvPPA) and the semantic variant PPA (svPPA), according to consensus classification (Gorno-Tempini et al., 2011). The PPA syndromes are associated with characteristic yet dynamic topographical changes in the structure and function of the brain associated with cognitive, mostly language, impairment(s) as previously shown in nfvPPA (Mandelli et al., 2016), svPPA (Agosta et al., 2013), and all three variants, as we recently documented (Tao et al., 2020). Earlier cross-sectional studies, including ours (Rogalski et al., 2007; Riello et al., 2018), did not provide support for any sex differences in PPA characteristics. However, recent studies show that sex may be a biological factor that differentiates progression of symptoms in PPA (Breining et al., under review). Importantly, studies in other neurodegenerative disorders, and Parkinson's Disease (PD) in particular, have shown sex differences in important aspects of language processing, such

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as morphology (Johari et al., 2019; Reifegerste et al., 2020; Ullman et al., 2008).

Currently, there is no pharmacological treatment, and the only interventions are traditional behavioral speech and language therapy and recent neuromodulatory approaches, transcranial direct current stimulation (active-tDCS) and transcranial magnetic stimulation (TMS) (Coemans et al., 2021; Cotelli et al., 2020; Nissim et al., 2020; Tippett et al., 2015). Language therapy paired with active-tDCS, a non-invasive neuromodulatory technique, has been shown to temporarily improve cognitive symptoms and slow language decline in patients with PPA (Cotelli et al., 2020), and generalize to untreated items or tasks (see Tippett et al., 2015; Cotelli et al., 2020; Nissim et al., 2020; Coemans et al., 2021 for reviews).

One of the big questions in responsiveness to therapy in general, and to active-tDCS in particular, is whether we can identify predictors of response to treatment. Several studies from our group and others have identified predictors of response to language therapy and active-tDCS in PPA. The particular predictors identified are: clinical, e.g., variants (Tsapkini et al., 2018); cognitive (de Aguiar et al., 2020); neural, e.g., volumetric (de Aguiar et al., 2020) and white-matter integrity (Zhao et al., 2021a); and behavioral, e.g., initial performance (de Aguiar et al., 2020; McConathey et al., 2017), and verbal learning ability (de Aguiar et al., 2020). In all these studies, however, effects were considered *independently* of several demographic or biological factors such as sex and age, by including these factors as independent variables in regression models, thus excluding their variance. However, recent evidence reviewed below advocates for a closer look at the effects of sex, a less studied variable in response to treatment in PPA. The present study addresses the role of sex as a moderator for brain network outcomes in response to language treatment, both with and without active-tDCS (referred to as sham-tDCS in the present study).

Characteristics of brain networks including FC may differ across the sexes: Differences in intra- and interhemispheric connectivity across regions of the default mode network (DMN), and the language-specific networks, have been observed between healthy men and women (Bluhm et al., 2008; Xu et al., 2015). Evidence from rsfMRI indicated that women have a more leftward asymmetry compared to men (Tian et al., 2011; Zhang et al., 2016). In PPA, we found higher global connectivity of the left IFG triangularis, a critical region involved in lexical processing (Bookheimer, 2002; Vigneau et al., 2006), for men prior to administering active-tDCS (Tao et al., 2022). The influence of demographics, however, is not always considered in treatment outcomes. Very few studies have investigated a possible differential effect of active-tDCS on FC or other measures in the two sexes (Bhattacharjee et al., 2020; Russell et al., 2017), see discussion in a recent review (Nissim et al., 2020).

With regard to active-tDCS mechanisms we know that active-tDCS facilitates synaptic transmission by modulating resting membrane potentials (Keeser et al., 2011). We and others have also shown that active-tDCS modifies functional connectivity (FC) in: healthy aging (Meinzer et al., 2012), cognitive impairment (MCI) (Meinzer et al., 2014); and PPA (Ficek et al., 2018a,b; Tao et al., 2021a,b). With regard to particular FC mechanisms, we and others have found that the FC changes that underlie active-tDCS effects in neurodegenerative disorders are reductions in connectivity and these reductions were correlated with treatment outcomes (Meinzer et al., 2012, Meinzer et al., 2013; Ficek et al., 2018a,b; Tao et al., 2021a,b). Furthermore, we also specified using graph-theoretical measures, that these reductions in connectivity due to active-tDCS but not sham-tDCS downregulated FC at the area of stimulation, the left inferior frontal gyrus (IFG) (Tao et al., 2021a,b). Higher global connectivity was significantly associated with dementia severity, as we and others found in PPA (Agosta et al., 2015; Mandelli et al., 2018; Tao et al., 2020), as well as in other neurodegenerative disorders (Bakker et al., 2012; Dickerson et al., 2005). Since reductions in connectivity following active-tDCS correlated with treatment outcomes, it was argued that these reductions may reflect higher processing efficiency of the language network. However, we do not know if sex modulates this downregulation in FC and whether this potential sex-modulated downregulation is network-specific in a language neurodegenerative disorder such as PPA.

In the present study we asked the question of how sex may moderate active-tDCS effects on FC. In other words, are active-tDCS effects on FC different between men and women, and how? In particular, we tested the hypotheses that: (i) downregulation of FC after treatment (active-tDCS or sham-tDCS combined with language therapy) in PPA is modulated by sex, (ii) downregulation of FC after active-tDCS is network-specific for each sex. Our aim was to explore patterns of active-tDCS treatment-induced FC changes in male and female patients with PPA within brain networks known to be language-specific (the language network, particularly affected in PPA) vs domain-general (the DMN, generally affected in neurodegeneration, AD and FTD). The consequences of sex-dependent modulation of an active-tDCS mechanism could not only alter the way we administer active-tDCS in the two sexes towards precision medicine, but also improve our understanding of the inherent possibilities or limitations of altering FC in the two sexes in other behavioral, pharmacological or neuromodulatory methods.

2. Materials and methods

2.1. Participants

Thirty-six patients with PPA participated in this study. Patients were recruited for a double-blind, sham-tDCS-controlled, randomized clinical trial (NCT02606422). Informed consent was obtained from participants or their spouses. All data were acquired in compliance with the Johns Hopkins Hospital Institutional Review Board (NA_00071337). These patients were diagnosed as one of three PPA variants (lvPPA, nfvPPA or svPPA) based on clinical, neuropsychological and language testing and MRI according to current consensus criteria (Gorno-Tempini et al., 2011). Participants were randomly assigned into two treatment arms: anodal active-tDCS over the left IFG ($n = 17$) and sham-tDCS ($n = 19$). Participants in both treatment arms were comparable with regard to overall clinical dementia rating, measured by the revised FTLD-CDR scale (see Table 1).

2.2. Active-tDCS application and language treatment

The active-tDCS methodology and application have been previously described (Ficek et al., 2018a,b; Tsapkini et al., 2018; Tao et al., 2021a, b). tDCS was delivered using Soterix 1x1 Transcranial Direct Current Stimulator Clinical Trials Model 1500. Current was delivered at 2 mA intensity (estimated current density 0.08 mA/cm2) for 20 min in the active-tDCS condition and 30 s in the sham-tDCS condition, according to manufacturer's ramping phase specifications. Nonmetallic, conductive rubber electrodes covered with saline-soaked 5 × 5 cm sponges were used to minimize the possibility of chemical reactions at the skin/electrode interface. The anodal site was the left frontal lobe, corresponding to the F7 electrode (left IFG), using the EEG 10–20 electrode position system (Homan, 1988). In addition, the IFG was individually co-registered to pretreatment MRI scans using a fiducial marker. The reference electrode, the cathode, was placed on the right cheek (see Ficek et al., 2018a,b; Tsapkini et al., 2018).

For both active-tDCS and sham-tDCS conditions, the electrical current was ramped up at stimulation onset, eliciting a transient (typically 30 s) tingling sensation. After ramping in the sham-tDCS condition, current intensity was decreased to 0 mA. Stimulation (for both conditions) started at the same time as language therapy. These procedures successfully blind participants to the assigned stimulation condition. Language therapy continued for another 20 to 25 min, and the therapist was blind to the stimulation condition. Participants were asked to report their general pain level once or twice during each session with the Wong-Baker FACES Pain Rating Scale (https://www.WongBakerFACES.

Table 1
(Demographics).

Subject	Treatment	Variant	Sex	# Sessions	Age	Language Severity	FTD-CDR
1	s	l	M	10	69	1	3.5
2	s	s	F	13	65	2	9
3	s	n	F	10	66	1	5
4	s	n	F	10	66	1	3
5	s	n	M	12	73	2	5
6	s	n	M	10	64	3	15
7	s	n	F	10	66	3	5
8	s	l	F	12	71	2	5
9	s	n	M	11	77	2	12
10	s	s	F	10	68	2	6.5
11	s	l	M	13	74	1	3
12	s	n	M	14	64	1	3
13	s	s	F	10	68	3	18.5
14	s	l	F	12	69	3	17
15	s	s	F	13	75	2	7.5
16	s	n	M	10	76	2	14
17	s	s	M	8	69	1	2.5
18	s	l	M	11	58	1	2.5
19	s	l	F	10	64	1	3.5
Mean		6 l, 8n, 5 s	9 M, 10F	11.00	68.53	1.79	7.39
SD				1.53	4.89	0.79	5.27
20	t	n	F	12	60	2	8
21	t	l	M	10	72	0.5	1.5
22	t	l	F	14	53	1	9.5
23	t	l	F	9	75	3	12
24	t	n	F	10	69	2	6
25	t	n	F	10	69	2	10
26	t	s	M	15	59	2	5.5
27	t	l	M	14	51	0.5	2
28	t	l	F	14	70	3	10
29	t	n	M	12	80	2	3
30	t	l	M	10	68	0.5	1
31	t	s	F	15	64	1	1
32	t	l	M	13	54	2	8
33	t	l	M	10	63	2	9.5
34	t	l	F	15	62	2	11.5
35	t	s	M	13	71	2	4
36	t	n	M	13	66	3	6
Mean		9 l, 5n, 3 s	9 M, 8F	12.29	65.06	1.74	6.38
SD				2.08	7.96	0.85	3.77
p-value		0.519	1.000	0.044	0.132	0.845	0.509

org). As stated in the main trial results (Tsapkini et al., 2018), in a scale of 1–10, the active-tDCS condition elicited mean pain ratings of 2.21 (SD = 2,48) whereas sham-tDCS elicited mean pain ratings of 2.14 (SD = 2.13). Behavioral therapy targeted oral and written word production with an emphasis on writing/spelling, as described in previous publications (Ficek et al., 2018a,b).

2.3. Resting-state fMRI data acquisition

Magnetization-prepared rapid acquisition gradient echo (MPRAGE) and resting-state functional MRI (rsfMRI) scans were acquired on a 3 Tesla Philips Achieva MRI scanner with a 32-channel head coil at the Kennedy Krieger Institute at Johns Hopkins University. Parameters of the T1-weighted MPRAGE sequence acquisition were the following: scan time of 6.5 min (156 slices); isotropic voxel dimension = 1*1*1mm; flip angle of 8°; SENSE acceleration factor of 2; FOV = 224*160*180 mm (ap, fh, rl); data matrix = 224*224*160; TR/TE = 8.1/3.7 ms (ms). Parameters of the rsfMRI acquisition were the following: scan time of 8.75 min (210 time-point acquisitions); FOV = 240*141*240 mm (ap, fh, rl); slice thickness of 3 mm; in-plane resolution of 3.3x3.3 mm2; flip angle of 75°; SENSE acceleration factor of 2; voxel dimension = 3*3*3mm; SPIR for fat suppression; data matrix = 80*80*47; TR/TE = 2500/30 ms.

We used MRICloud, a multi-atlas, automated image parcellation approach, to parcel the MPRAGE scan into 283 segments, using multi-atlas fusion label algorithm (MALF) and large deformation diffeomorphic metric mapping (LDDMM) (Ceritoglu et al., 2013; Miller et al., 2005). Mapping inaccuracies because of atrophy or local shape deformations were reduced with this highly accurate diffeomorphic algorithm. Preprocessing involved standard routines from the SPM connectivity toolbox for co-registration, motion and slice timing correction; physiological nuisance correction using CompCor (Behzadi et al., 2007) and motion and intensity TR outlier rejection using "ART" (https://www.nitrc.org/projects/artifact_detect/). To correct for motion, ART detected outliers and a motion matrix was generated; these were used in combination with the physiological nuisance matrix in the deconvolution regression for the remaining TRs. Full details are described in a previous publication (Faria et al., 2012).

Resting-state fMRI scans were also processed in MRICloud, then co-registered with MPRAGE scans into the same anatomical space. All analyses were done in native space. Average time courses of all voxels for 78 different regions of interest (ROIs) were extracted and normalized. Correlations between region pairs were calculated and transformed with the Fisher z-transformation.

In this study, nineteen brain regions were analyzed which comprise the language and default mode network in most studies. Bilaterally, we analyzed the IFG opercularis, IFG orbitalis, IFG triangularis regions, as well as the middle frontal gyrus (MFG)/dorsolateral prefrontal cortex (dlPFC), angular gyrus (AG), and posterior cingulate cortex (PCC); within the left hemisphere only, we examined the supramarginal gyrus (SMG), fusiform gyrus (FuG), superior temporal gyrus (STG), STG pole, middle temporal gyrus (MTG), MTG pole, inferior temporal gyrus (ITG).

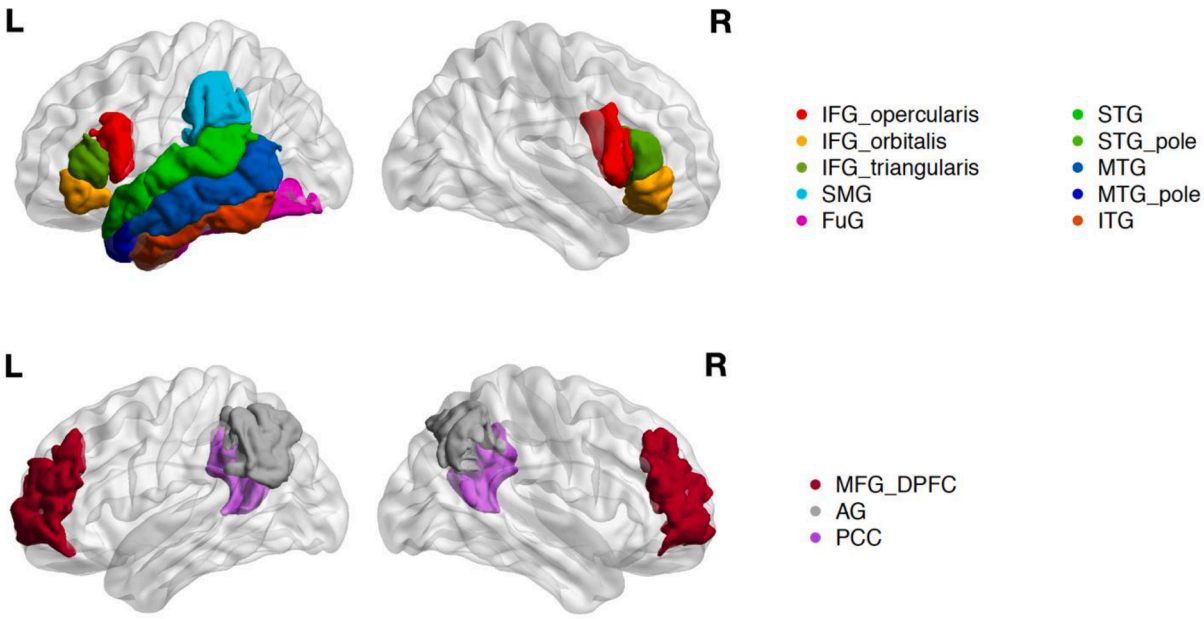


Fig. 1. Brain regions included in the study.

Fig. 1 presents these regions in a brain map.

2.4. Statistical method

We implemented the covariate assisted principal (CAP) regression introduced by (Zhao et al., 2021b) on the post-intervention rsfMRI data from this RCT to evaluate the active-tDCS effect on resting-state FC, as well as the heterogeneity in the active-tDCS effect between male and female participants. The CAP method aims to identify brain subnetworks facilitating subject-specific characteristics. It overcomes the issue of statistical power loss in pair-wise analysis with multiple comparisons correction. The method generalizes a regression model to the setting that the outcome is a covariance matrix instead of a scalar. For subject i ($i = 1, \ldots, N$), let $y_{it} \in \mathbb{R}^p$ denote the blood-oxygen-level-dependent (BOLD) signal collected from p brain regions at the tth scan ($t = 1, \ldots, T_i$, where T_i is the number of scans of subject i), which is assumed to be normally distributed with mean zero and covarianceΣ_i . Let $x_i \in \mathbb{R}^q$ denote a q-dimensional vector of covariates (here the first element of $\mathbf{x}_i$ is one for the intercept term). The CAP method assumes that there exists a linear projection$\gamma \in \mathbb{R}^p$, such that

$$\log\left[Var\left(\gamma^T y_{it}\right)\right] = \log\left[\gamma^T \Sigma_i \gamma\right] = x_i^T \beta,$$

where β is the model coefficient. In rsfMRI studies, after standardizing the BOLD time courses, the covariance matrix is generally utilized to reveal the coherence level between brain regions (the so-called functional connectivity). The linear projection or the component infers the coherently active brain subnetworks (Poldrack, 2011). With a significant model coefficient, the FC within the brain subnetwork is associated with the corresponding covariate. In order to determine the number of components, a metric called the average deviation from diagonality was introduced for multiple covariance matrices. As suggested, one can plot the value of this quantity and choose an appropriate number of components. In this study, we used the suggested threshold of two in Zhao and colleagues (Zhao et al., 2021b) to decide the number of components.

We applied this method to the first post-therapy (before crossover) rsfMRI data and reported treatment and sex group differences in FC (see the same analysis in pre-therapy data in Supplementary Materials). We considered a model with the interaction between treatment assignment (active-tDCS vs sham-tDCS in the first period of therapy) and sex to study the heterogeneity. We included variant type, age, and language severity (as measured by the FTLD-CDR scale) in the model to adjust for potential confounding effects. For model coefficients, 95 % confidence intervals were acquired from 500 bootstrap samples. The method was implemented using the R package cap available on Comprehensive R Archive Network (CRAN). In the supplementary materials, robust regression models were fitted for the change in behavioral outcomes post- and pre-treatment to examine the group differences and Tukey's procedure was employed for multiple comparisons. The models included treatment assignment, sex, and their interaction, as well as variant type, age, and language severity, as the predictors.

3. Results

The CAP model identifies brain networks whose FC is associated with the covariates of interest. All effects reported constitute changes from the pre-interventional FC, shown in Supplementary Materials. In an identified component, the FC between regions with loadings in the same direction (i.e., both positive or both negative) changes towards the sign of the coefficient. Conversely, the FC between regions with loadings in the opposite direction (i.e., one positive and one negative) changes towards the opposite sign of the coefficient. The CAP method identified two components (C1 and *C*2) representing different networks (Table 2 and Figs. 2 and 3).

3.1. Effects of active-tDCS on FC of the DMN (Component 1)

The first component (C1) loaded highly on regions that belong to what has been identified as the DMN (or even a multiple-demand network, (Fedorenko et al., 2012), including the left/right dlPFC, the left/right angular gyrus (AG), and the right posterior cingulate cortex (PCC). We found a significant active-tDCS effect among men and a significant sex difference within the sham-tDCS group in this component.

In DMN (C1), FC in men who received active-tDCS was significantly different from FC in men who received sham-tDCS (coefficient = 0.742, SE = 0.229, p-value = 0.001; see Table 2) in the following aspects: men who received active-tDCS exhibited higher FC between right PCC and right dlPFC (regions with loadings in the same direction, see Fig. 2) and lower FC between homotopic regions, i.e., right and left AG and between right and left dlPFC (regions with loadings in the opposite direction, see Fig. 2).

Furthermore, DMN (C1) FC in men was significantly different from

Table 2
The estimated model coefficient and 95% bootstrap confidence interval of the two identified components. (SE: standard error; CI: confidence interval).

Component		Estimate (SE)	95 % CI	*p*-value
C1	active-tDCS-sham-tDCS (Female)	−0.073 (0.248)	(−0.559, 0.413)	0.769
	active-tDCS-sham-tDCS (Male)	0.742 (0.229)	(0.293, 1.190)	0.001
	Male-Female (sham-tDCS)	−0.873 (0.244)	(−1.351, −0.395)	<0.001
	Male-Female (active-tDCS)	−0.058 (0.220)	(−0.489, 0.373)	0.792
	Age	0.006 (0.112)	(−0.018, 0.029)	0.635
	Language Severity	−0.176 (0.122)	(−0.415, 0.063)	0.148
	Nonfluent-Logopenic	−0.022 (0.179)	(−0.373, 0.329)	0.902
	Semantic-Logopenic	−0.426 (0.253)	(−0.922, 0.071)	0.093
	Semantic-Nonfluent	−0.404 (0.264)	(−0.922, 0.115)	0.127
C2	active-tDCS-sham-tDCS (Female)	−0.761 (0.165)	(−1.084, −0.437)	<0.001
	active-tDCS-sham-tDCS (Male)	−0.258 (0.216)	(−0.681, 0.164)	0.231
	Male-Female (sham-tDCS)	−0.284 (0.184)	(−0.646, 0.077)	0.123
	Male-Female (active-tDCS)	0.218 (0.178)	(−0.131, 0.568)	0.221
	Age	−0.028 (0.010)	(−0.048, −0.007)	0.009
	Language Severity	0.125 (0.082)	(−0.035, 0.285)	0.127
	Nonfluent-Logopenic	−0.126 (0.123)	(−0.368, 0.115)	0.306
	Semantic-Logopenic	0.012 (0.209)	(−0.397, 0.422)	0.953
	Semantic-Nonfluent	0.139 (0.224)	(−0.301, 0.578)	0.536

that in women in the sham-tDCS group (coefficient = -0.873, SE = 0.244, *p*-value < 0.001; see Table 2) in the following aspects: men exhibited higher FC between homotopic regions, right and left AG and between right and left dlPFC (regions with loadings in the opposite direction, see Fig. 2) and lower FC between right PCC and right dlPFC (regions with loadings in the same direction, see Fig. 2).

3.2. Effects of active-tDCS on FC of the language network (Component 2)

The second component (C2) loaded highly on regions that belong to what has been identified as the language network including the stimulated area of left IFG, left superior (middle and posterior) temporal gyrus (STG), left inferior temporal gyrus (ITG), left fusiform gyrus (FuG), and right dlPFC. We found a significant active-tDCS effect in women, as well as a significant association with age. No effects in homotopic connectivity were observed.

In the language network (C2), FC in women who received active-tDCS was significantly different from FC in women who received sham-tDCS (coefficient = −0.761, SE = 0.165, *p*-value < 0.001; see Table 2) in the following aspects: they exhibited lower FC between left IFG and left STG and ITG (regions with loadings in the same direction, see Fig. 3) and higher FC between the following left areas (IFG, STG, ITG) and areas including the left FuG and STG_pole (regions with loadings in the opposite direction, see Fig. 3).

Furthermore, in the language network (C2), FC was significantly associated with age (coefficient = −0.028, SE = 0.010, *p*-value = 0.009, see Table 2) in the following way: older people exhibited lower FC between left IFG and left STG and ITG (regions with loadings in the same direction, see Fig. 3) and higher FC between the following left areas (IFG, STG, ITG) and areas including the left FuG and STG_pole (regions with loadings in the opposite direction, see Fig. 3). No effects in homotopic connectivity were observed.

3.3. Effects of variant type, language severity, and age

For both identified components, no significant effects of variant type or language severity on FC was observed. In C2, the effect of age on FC is significant and negative (coefficient = −0.028, SE = 0.010, *p*-value = 0.009) suggesting that as age increases, FC in the language network decreases. No significant age effect was observed on the FC in DMN in C1.

4. Discussion

In the present study we asked the question whether biological differences, such as sex, moderate effects of active-tDCS on FC in patients with PPA. We utilized data from anodal active-tDCS over the left IFG in a group of patients with PPA to evaluate whether changes in FC (from rsfMRI) following active-tDCS and sham-tDCS interventions differ between female and male participants. We analyzed nineteen brain regions across the language and default mode networks using a novel regression method, the CAP regression model, that can reveal data-driven subnetworks and their interaction with other variables, such as age (Zhao et al., 2021b). Differences in network connectivity and variations in the response to active-tDCS were found between men and women. In the DMN (C1), we found a significant active-tDCS effect in men only such that men who received active-tDCS had higher FC between right hemisphere regions of DMN but lower FC between homotopic AG and dlPFC; moreover, we found that men who received sham-tDCS showed higher FC in homotopic AG and dlPFC of DMN compared to women who received sham-tDCS. In the language network (*C2*), we found a significant active-tDCS effect in women only: women who received active-tDCS had lower FC between the IFG and other language areas of the left hemisphere (STG, ITG). Although FC in women who received active-tDCS was different from those who received sham-tDCS even at baseline, i.e., before treatment, the post-treatment difference between active-tDCS and sham-tDCS in women is significantly larger compared to pre-treatment (the post-treatment confidence interval [CI: (−1.084, −0.437), p < 0.001] clearly does not include the pre-treatment estimate of −0.426). Given that this is a randomized trial, the pre-treatment difference may be due to the small sample size and subsequent imbalance. Moreover, we found a significant age effect, suggesting that older individuals exhibit lower FC than younger individuals in the language network. (Note that there was no difference between men and women in either active or sham-tDCS active-tDCS groups for variant type, number of sessions, age and language severity, please see Table S3). Below we discuss these results considering previous effects of active-tDCS on FC and the effects of neurodegeneration in FC as documented in the literature.

In the field of neurodegeneration, higher FC in patients compared to healthy aging is a common finding and has been interpreted as either a consequence of neurodegeneration or as a compensatory mechanism of the brain in response to neurodegeneration (Bakker et al., 2012; Dickerson et al., 2005). While the DMN spans both hemispheres and is known to be aberrant in both AD (Grajski, 2020; Seeley et al., 2009) and FTD (Malpetti et al., 2019), the language network is predominately left-lateralized in most individuals and its functional segregation is both dynamic across the lifespan in healthy individuals (Zuo et al., 2010) and severely impacted in PPA. Although we (Tao et al., 2021a,b) and others (Agosta et al., 2013; Mandelli et al., 2016) have not found any direct evidence of correlation between atrophy and FC changes in PPA, higher FC has always been regarded as either prodromal to disease or a disease condition per se. Our previous study has shown that men with PPA had higher global connectivity for the left IFG (the stimulated area) at

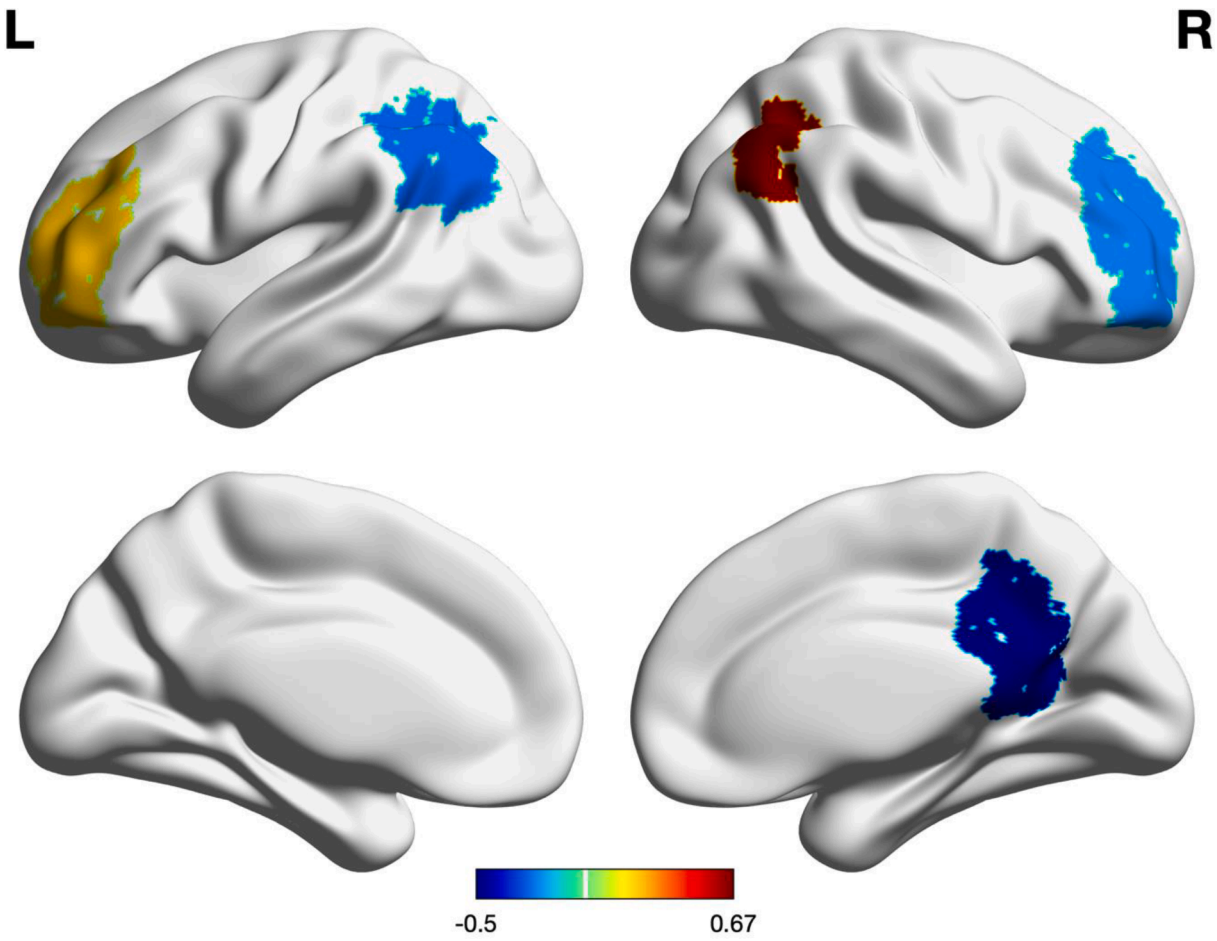
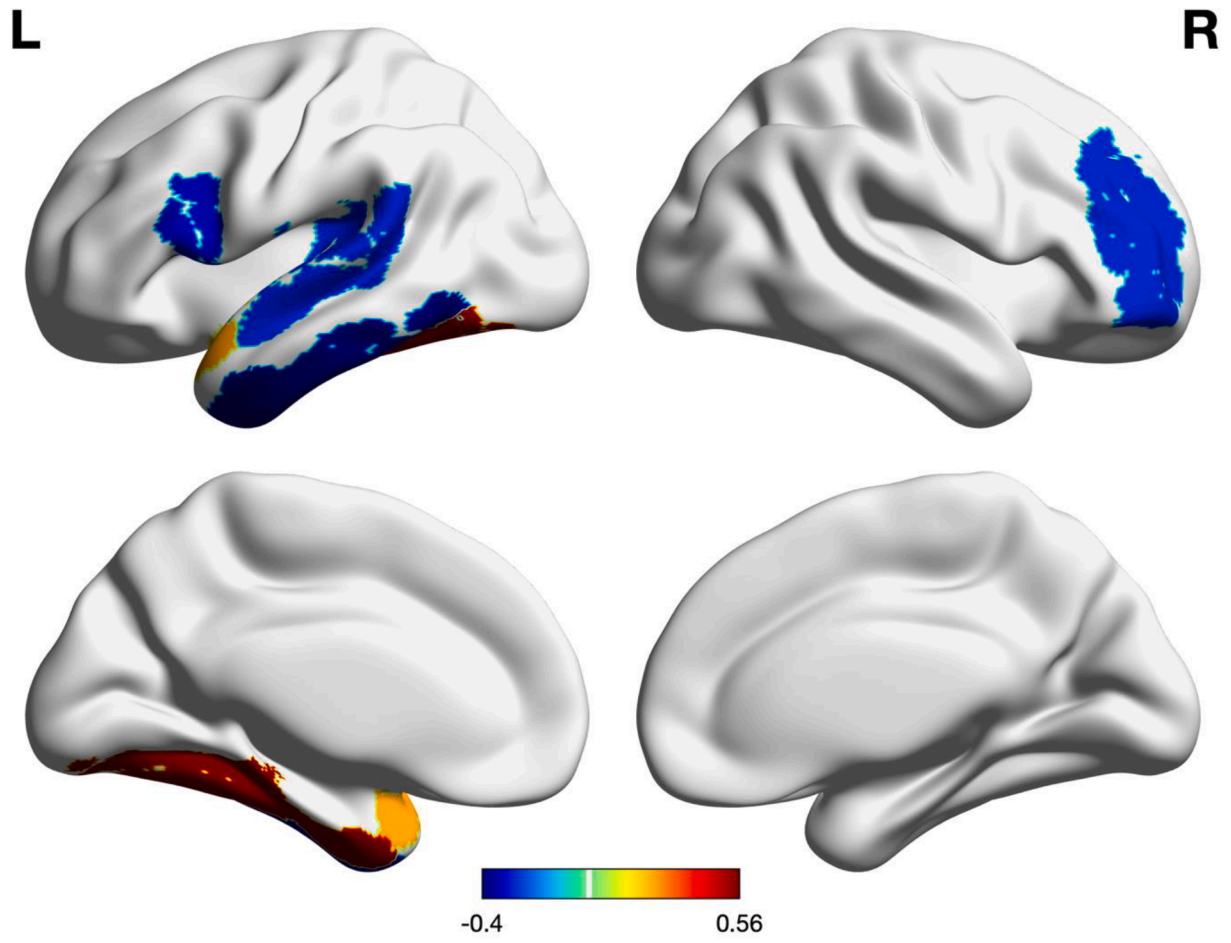


Fig. 2. Brain regions with high loading magnitude in DMN, the identified Component 1 (C1), (red: positive, blue: negative) loadings in C1.

baseline (Tao et al., 2021a,b), which is in line with previous literature in healthy controls showing sex differences in FC (Tian et al., 2011; Zhang et al., 2016). In a recent study, we found that homotopic FC between the whole left and right hemispheres is abnormally high in PPA compared to healthy controls (Tao, n.d.). Importantly, higher FC within each hemisphere was significantly correlated with worse performance in global dementia scores, such as FTD-CDR scale (Tao et al., 2020) and higher between- hemispheres (homotopic) FC was significantly correlated with general executive decline in cognitive tasks, such as Trail B (Lezak et al., 2004; Tao, n.d.). In this light, the present finding that men who received active-tDCS exhibited significantly greater FC reductions in homotopic regions of the DMN (AG and dlPFC) than men who received sham-tDCS suggests that active-tDCS may have induced a normalization of a global cognitive deterioration, particularly for men.

With regard to the effects of active-tDCS in aging and neurodegeneration, previous research from our group on PPA (Ficek et al., 2018a,b; Tao et al., 2021a,b) as well as others on healthy aging (Sheng et al., 2018), and MCI (Meinzer et al., 2015; Meinzer et al., 2013), have shown significant decreases in FC following active-tDCS stimulation. These decreases were deemed to be a compensatory strategy following brain damage in functionally-specific regions, such as those involved in the language network during recovery (Brownsett et al., 2014; Geranmayeh et al., 2016). Interestingly, this notion was reflected in the language network for women in the present study, i.e., women who received active-tDCS exhibited lower FC between language areas, and importantly, between the stimulated area (left IFG) and other areas of the language network (left STG, ITG). The significant sex-active-tDCS effect for women within our language network could thus reflect several phenomena: 1) greater preservation of language network connectivity (which supports active-tDCS-treatment outcomes) in women, 2) compensatory "hubs" within the language network or 3) hyperactivity of the language system which is normalized via active-tDCS treatment. Specifically, women who received active-tDCS showed reduction in FC between the left IFG and left temporal areas. The right dlPFC region also showed reduced FC with the left inferior frontal and superior temporal areas, suggesting greater normalization of both within and between-network connectivity following active-tDCS treatment, as the right dlPFC and inferior frontal regions belong to both the DMN and the multiple demand network (MDN; see (Duncan, 2010). As language ability and associated brain networks deteriorate over time, domain-general regions (including those of the DMN) may be recruited during language processing as a compensatory mechanism (Hartwigsen, 2018). It is plausible that men in our cohort recruited more domain-general regions outside of the language network to compensate for language processing and active-tDCS normalized this demand. Moreover, for men in the active-tDCS condition, within- and between-network (homotopic) connectivity could have mediated the effects of anodal active-tDCS treatment, which led to a greater normalization of between-network (homotopic) connectivity for men post-treatment. Greater inter-hemispheric connectivity found previously in healthy men (Bluhm et al., 2008) and greater global connectivity in men with PPA (Tao et al., 2021a,b) may support the cortical spread of active-tDCS treatment effects via sex-dependent brain networks that may underlie this potential difference.

Although research regarding sex-based differences in active-tDCS with and without language therapy in PPA is scarce, a previous study has noted a greater benefit from active-tDCS intervention in bilingual men compared to women in reading (Bhattacharjee et al., 2020) and a



(a)

Fig. 3. Brain regions with high loading magnitude in the language network, the identified component 2 (*C*2), (red: positive, blue: negative) loadings in *C*2.

recent *meta*-analysis examining non-invasive brain stimulation (NIBS) in PPA suggests that women may have greater language benefits than men (Nissim et al., 2020). A possible reason for differences in active-tDCS effects between men and women could be related to different brain anatomy or even skull properties between the two sexes, since men and women have different bone density and cranial resistance in several areas of their skull, different gray matter density and cortical thickness (Bhattacharjee et al., 2020; Russell et al., 2017). Furthermore, the association of synaptic proteins, such as brain derived neurotrophic factor (BDNF), to estrogen and aging, suggests that women may experience steeper declines in BDNF with age due to estrogen declines. FC differences between men and women are modulated by sex hormones, such as estrogen, and by the expression of BDNF, a synaptic protein involved in neural growth, survival, and synaptic conductivity and plasticity (Boyuk et al., 2014; Morales-Marín et al., 2016). BDNF levels are positively correlated with estrogen in women (Chan and Ye, 2017; Dong et al., 2017) and decrease across age. Interestingly, BDNF has been associated with FC changes (Gorka et al., 2019; Woelfer et al., 2020) and active-tDCS neuromodulation (Fridriksson et al., 2018), which may rely upon BDNF secretion to mediate synaptic plasticity (Fritsch et al., 2010). BDNF is commonly associated with the extent of cognitive decline, namely in AD and FTD populations, and may modulate pathological spread of neurodegenerative diseases (Goetzl et al., 2018, 2016; Lu et al., 2013). Val66Met, a common single-nucleotide polymorphism in the human BDNF gene causing a valine-to-methionine substitution, has been associated with the vulnerability, prevalence and clinicopathology of several disorders including AD (Shen et al., 2018). Reduced BDNF levels are also observed in populations at risk for AD and FTD (Goetzl et al., 2016). The evidence that active-tDCS is affected by BDNF expression genes, and in turn affects BDNF levels and FC, explains why sex may moderate active-tDCS effects on FC. Furthermore, the finding of the present study that behavioral treatment alone (sham-tDCS condition) led to increased FC between DMN regions for men but not women explains why sex may moderate language treatment effects on FC.

The present study also sheds some light on the interaction of active-tDCS with aging. We found that active-tDCS lowered FC in older compared to younger participants (range 50–85 years) across regions of the language network. The age effect we see in our language network may reflect the aberrant functional segregation of this network in the eldest of PPA patients, who are potentially at a more advanced stage of their disease, warranting greater compensation. The oldest PPA patients could have had more severe atrophy than younger PPA patients and, there was a positive correlation between age and language severity (Kendall's tau = 0.163, p-value = 0.220), though not significant. Furthermore, atrophy has not been shown to correlate with FC, as we and others have shown (Agosta et al., 2013; Mandelli et al., 2016; Tao et al., 2020), but it could be related to white-matter abnormalities, particularly in the white matter pathways connecting homotopic connectivity that are involved in the DMN (e.g. corpus callosum, arcuate and uncinate fasciculi). This is important because FC, namely in the

DMN, has been found to reflect structural connectivity (Greicius et al., 2009). Although beyond the scope of the present study, an analysis of structural connectivity in relation to FC could shed more light in the present effects of age.

4.1. Limitations

Some limitations of the present study include the lack of investigation of the role of the specific factors related to sex differences. We did not investigate, for example, where sex differences may come from, e.g., skull differences, hormonal differences, or genetic differences. Future active-tDCS studies should examine effects of skull density and other physiological factors that influence the amount of cortical current that is actually received upon active-tDCS administration to ensure consistency across subjects. We could use e-field modeling for the current density of the male and female groups to see if the FC changes correlate with e-field. However, we do not have e-field for all patients in the current study because it requires a longer scan with special parameters that were not included in our protocol. Members of our team have used alternative methods, in a recent paper (Bhattacharjee et al., 2022). We could potentially model our montage and look at group differences in regional active-tDCS current density, as was done in that paper. Bhattacharjee et al., showed age-dependent sex differences in regional active-tDCS current mediated by changes in cortical anatomy, which supports the plausibility of the speculation in our paper that anatomical differences could underlie sex differences in FC induced by active-tDCS. But to perform this modelling in the present cohort and then try to correlate current density differences with FC changes would be an entire project that is beyond the scope of the present paper. However, this could be the subject of a future paper. A larger sample of patients is needed to validate the current findings; in the current study, we did not examine the PPA variants separately in our model due to a lack of power (sample size of 36 patients). Given the significant effect of aging seen in *C*2 in this study, greater power in future analyses utilizing the CAP model could expand on this finding and examine interactions between aging and sex, potentially through quantitative measurements of sex steroids, e.g., hormonal balances. We should also note that although the treatment was personalized, i.e., items were chosen for each patient, current intensity and duration were not personalized because there is not an easy and validated criterion to apply for adjusting active-tDCS intensity. We are working towards more personalized treatments which we aspire to implement in the future. In the present study we did not report the possible effect of medications of the participants. Since there are no disease modifying mechanisms in PPA and it is not clear from the literature whether other types of medications affect rsfMRI scans, this parameter was not included. Although some participants may have been taking SSRIs or other depression medication, this was not grounds for exclusion in the current study. It is not yet clear whether SSRIs influence active-tDCS or rsfMRI scans, and we did not gather this information systematically during recruitment, however this is an important point for future research. Another limitation of this study is that we did not investigate whether sex differences interact with FC differently across PPA variants. In the present study, the data-driven networks were identified with regard to sex. However, if variant is an important factor for language outcomes as we have previously found, we would need to identify brain networks with regard to variant first. Future studies should consider these limitations when designing studies focused on sex differences in tDCS treatment.

5. Conclusion

The present study describes the sex differences in FC associated with active-tDCS using a robust, network-level approach and suggests that these sex differences may be network-specific. The current study emphasizes that active-tDCS treatment in PPA alters network-specific FC in a sex dependent manner and lays groundwork for further examination of sex-driven differences in responsiveness to and outcomes of active-tDCS-therapy. This study is the first to examine neuromodulation effects and their interaction to demographics, such as sex and age. Our findings suggest that women have greater responsiveness to left-hemisphere active-tDCS across language-associated regions flattening the trajectory/slope of declining processing efficiency in women for this network. Perhaps because this network still retains greater functional segregation in women with PPA compared to men despite aberrant connectivity resulting from pathology. Right hemisphere active-tDCS stimulation sites should be considered when examining language FC, particularly in older and late-onset dementia cohorts, given the compensatory mechanisms of other regions/networks following language network damage. Within domain-general regions a part of the DMN, we found a greater responsiveness following active-tDCS in men as well as baseline differences in DMN FC between the sexes, suggesting network-specific differences underly active-tDCS responsiveness in men and women with PPA. Future research should consider structural confounds such as gray-matter volumes, cranial resistance, and atrophy levels in their active-tDCS methodology, as they can mediate the effects of active-tDCS. Our work cautions researchers to examine sex differences on a global scale, as network-specific changes may better highlight sex, rather hormonal, differences in PPA individuals.

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CRediT authorship contribution statement

Abigail E. Licata: Conceptualization. **Yi Zhao:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization. **Olivia Herrmann:** Data curation. **Argye E. Hillis:** Conceptualization, Investigation, Methodology. **John Desmond:** Conceptualization, Investigation, Methodology. **Chiadi Onyike:** Conceptualization, Investigation, Methodology, Supervision. **Kyrana Tsapkini:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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All authors have reviewed the contents of the manuscript being submitted, approved its contents, and validated the accuracy of the data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103329.

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