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Resting-State EEG Alteration Over the Loreta *Z*-Score Neurofeedback in Aphasia

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Abstract

Objectives. Aphasia is an acquired language disorder resulting from a brain injury which affects the brain's electrical activity. Neurofeedback (NFB) is known to synchronize neural oscillations and normalize brain wave abnormalities in several disorders. In this study, we aimed to investigate EEG signals in aphasia and the possible positive effect of Loreta *z*-score neurofeedback (LZNFB) treatment on improving EEG disturbances and symptoms in aphasia. **Methods**. Thirteen chronic aphasics and 10 unimpaired nonaphasic subjects were investigated in this study. Clinical assessments were used for the aphasic group at baseline and after 15 sessions of LZNFB to illustrate behavioral improvement. To estimate signal disruption and its alteration over the treatment, EEG signals were acquired referred to as resting-state eyes-closed condition in aphasic group during pretreatment and posttreatment as well as in the nonaphasic control group. We then investigated brain complexity and phase-amplitude coupling (PAC) in groups and compared the results. **Results**. Our EEG findings were congruent with clinical improvement and showed that after treatment, complexity and PAC changed to a normal level. **Conclusion**. We conclude that LZNFB treatment was effective in decreasing EEG disturbances and symptoms in aphasia. We think that our findings in complexity and PAC could provide important insights into the electrophysiological profile in aphasia and its alterations after treatment.

Keywords: aphasia; phase-amplitude coupling; complexity; neurofeedback; loreta

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Introduction

Aphasia is a clinical syndrome characterized by progressive speech and language deficits caused by selective neurodegeneration of particular brain networks. Several studies reported brain abnormalities in aphasia. For example, increased delta and theta activity in damaged linguistic regions within the left hemisphere of a patient with different aphasic diagnostic has been reported in previous studies (Szelies et al., 2002). It has been shown that increased delta and theta activity in aphasia can also affect EEG signal complexity (Shah-Basak et al., 2020; Takahashi et al., 2010). Wu et al. (2015) estimated approximate entropy (ApEn) in aphasia and showed higher complexity in the left hemisphere. On the other hand, phase-amplitude coupling (PAC), which is shown to be associated with brain processing (Canolty & Knight, 2010), is also reported as an aberrant feature in aphasia. Liu et al. (2019) applied the PAC algorithm to investigate multimodal neuro signals including CBF and EEG in stroke aphasia, estimated the hemispherical asymmetry of PAC, and compared the differences between the left and right hemispheres. Their result showed excessive PAC at the left occipital region in aphasia. They also analyzed PAC in the survival group as compared to the deceased group and found the deceased group showed smaller PAC than the survival group. Moreover, they showed that the PAC asymmetry between two brain hemispheres correlates with the degree of disorder.

EEG in patients with aphasia can also be distinguished from healthy controls by measuring differences in the functional connectivity of resting

networks (Marebwa et al., 2017; Yang et al., 2018). Shah-Basak et al. (2020) estimated brain network connectivity and reported reduced left hemisphere connectivity in aphasia. On the other hand, neuroimaging studies investigated brain connectivity in aphasia and its alteration during recovery. Nicolo et al. (2015) associated the coherence of neural oscillations in language networks with clinical improvement. The authors showed that the beta-band weighted node degree at the ipsilesional (Broca) area was correlated with better language improvement. Recovery was further associated with contra-lesional theta band weighted node degree (Nicolo et al., 2015). It is observed that the magnitude of alpha-band functional connectivity is correlated with behavioral performance in stroke aphasia patients (Mottaz et al., 2018). Another study investigated the association between the brain's structural connectivity and recovery and found anterior temporal connectivity can predict future recovery (Warren et al., 2009).

As aphasia lowers functional independence and health-related quality of life and increases the vulnerability to other diseases such as cancer, Alzheimer's, and Parkinson's (Lam & Wodchis, 2010), there is a need to improve currently available therapeutic options for aphasia. Neuromodulation, represented by neurofeedback (NFB), has been known as a potential therapeutic modality for many years. It uses real-time displays of electroencephalogram (EEG) to illustrate brain activity and allows for self-regulating brain activity by diminishing excessive fast or slow waves, which may frequently be seen in several disorders (Mottaz et al., 2018; Ramot et al., 2017). Growing evidence shows that NFB generates oscillations extending to distinct brain areas, such as the cortical and subcortical regions (Bichsel et al., 2021; Nicholson et al., 2016; Ros et al., 2014). Several studies show the effectiveness of NFB both behaviorally and at the network level (Cortese et al., 2017; Enriquez-Geppert et al., 2019; Grin-Yatsenko et al., 2018; Hirano & Tamura, 2021; Koush et al., 2017). Moreover, previous case studies reported the efficiency of NFB in the reduction of aphasia symptoms (Mroczkowska et al., 2014; Nan et al., 2019; Rozelle & Budzynski, 1995).

Low-resolution electromagnetic tomography analysis (LORETA) *z*-score NFB (LZNFB) has been introduced to the market relatively recently (Applied Neurosciences, Inc., USA). This system has the potential to provide faster results due to the application of a larger number of electrodes during treatment (Koberda et al., 2012). Furthermore, it can receive instant comparisons using a reference database of healthy individual *z*-scores. These instant comparisons enable finding a link between patients' symptoms and Brodmann areas (BA) in the brain (Thatcher, 2010). This technology has recently been shown to be an effective treatment for many neuropsychiatric disorders and cognitive dysfunction (A. Faridi et al., 2022; Frey & Koberda, 2015; Koberda, 2014, 2015; Prinsloo et al., 2019). Our recent case report (F. Faridi et al., 2021), suggested the potential of LZNFB in language rehabilitation for a TBI aphasia.

To date, much work has focused on local dysfunction in aphasia, but so far little is known about the electrophysiological abnormalities in aphasia and its alteration after NFB treatment as compared to a healthy control group. In this study, we aimed to estimate EEG disturbances in aphasia and possible improvement in EEG abnormalities and symptoms over the LZNFB treatment. To this end, we acquired clinical assessment in the aphasia group at baseline and after 15 sessions of treatment. We also investigated EEG signals, referred to as the resting-state eyes-closed condition in the aphasia group (during pre- and posttreatment) as well as in the nonaphasia control group. Then we analyzed EEG complexity and PAC and compared the results in groups. The hypothesis of the current study is as follows:

- Increased complexity and decreased PAC are shown in aphasia as compared to the nonaphasic group.
- Increased complexity and decreased PAC in aphasia change to nonaphasic control group level after LZNFB.

Materials and Methods

Participants

The study group included 13 aphasic patients (five females and eight males with ages of 46.53 ± 12.95 and 10 nonaphasic control individuals (four females and six males with ages of 34.46 ± 5.99). Aphasic patients were selected according to the following criteria: a) they had been diagnosed as nonfluent aphasic patients during the acute phase (Table 1), and b) at the time of the study, all patients had to be in a chronic state, as attested by an average time from the lesion of 27.84 ± 5.55 months (range: 7–60 months).

Table 1

Patient's Demographic Data, Along With the Severity of Their Condition, Etiology, Post-Onset, Lesion Location, Education, Gender, and Age

Name	Severity	Etiology	Post-onset (months)	Lesion location	Education (years)	Gender	Age
MA	Moderate	Stroke	10	Left frontal	5	Female	57
AZ	Mild	Stroke	25	Left frontal	12	Male	58
MM	Moderate	Stroke	12	Left frontal	12	Female	56
ZB	Mild	Stroke	8	Left frontal	2	Female	58
PF	Mild	Trauma	11	Left frontal	14	Male	22
HS	Medium	Stroke	18	Left frontal	5	Male	53
FA	Mild	Stroke	19	Left frontal	12	Female	48
FK	Mild	Trauma	48	Left frontal	16	Male	34
HA	Mild	Trauma	60	Left frontal	12	Female	50
MK	Mild	Trauma	60	Left frontal	7	Male	23
MR	Severe	Trauma	48	Left frontal	14	Male	38
AM	Mild	Stroke	36	Left frontal	12	Male	54
NO	Mild	Stroke	7	Left frontal	12	Male	54

Ethical Statement

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished and, if desired, the research results would be available to them. Written informed consent was provided by patients' next of kin. The study was approved by the Ethics Committee at Tarbiat Modares University (IR.MODARES.REC.1400.249).

Intervention

The EEG was recorded from 19 scalp locations based on the international 10-20 system of electrode placement and the linked ear as a reference. These electrodes positions were Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz. Recordings were sampled at 256 HZ. The qEEG data were collected using a Medicom amplifier and the EEG Studio Acquisition software. Editing and digital analysis of the qEEG data were carried out using NeuroGuide software and comparative databases. The protocol included LZNFB within the language network. In the language network, BA included 22, 39, 40, 41, 42, 44, and 45. Moreover, learning reinforcement in NFB was provided using television shows or animations that increased in size when meeting the defined difficulty thresholds.

EEG Analysis

In this study, we used five indexes of complexity in time series which are described as the following: Katz, Higuchi, Sevcik, spectral entropy (SpEn), and approximate entropy (ApEn).

Fractal dimension (FD) analysis was performed using MATLAB on EEG data. FDs reflect the chaotic character of nonlinear signals and also show complexity and self-similarity in EEG signal. In this study, we used four indices of FDs, SpEn, and ApEn. Therefore, 10-s duration of the EEG channels for each index was taken. We finally computed the average of all windows.

Katz's Fractal Dimension (KFD). One of the algorithms to calculate the FD and complexity of a one-dimensional time series is KFD which is calculated by the distance between two successive points (Katz, 1988; Salimi et al., 2022; Sho'ouri et al., 2019).

$$\mathrm{KFD} = \frac{\log(N)}{\log(N)+\log(\frac{d}{L})}$$

Where the maximum distance from the first point is measured as *d* computed as following:

$$d = \max\left(|x1 - xj|\right) ; \mathrm{j} = 2, 3, \ldots, \mathrm{N}$$

and the total length of the time series taken as

$$L = \sum_{(i=2)}^{N} X_i - X_{i-1}$$

Higuchi's Fractal Dimension (HFD). Another known way to calculate the FD of time series is HFD (Mohammadi et al., 2016) in which the original time series is defined as

$$X_m^k = X(m).X(m+k).X(m+2k). \ldots X(m+int(\frac{N-m}{k}) \times k$$

Where N is the length of the time series, m showed the initial time, and k denotes the interval time. We consider k_{max} = 20 for this study. Accordingly, the length $L_m(k)$ of the curve X_m^k is computed as follows:

$$L_m(k) = \frac{\sum_{i=1}^{int(\frac{N-m}{k})} |X(m+ik) - X(m+(i-1)k| \times (N-1)}{k \times int\left[\frac{N-m}{k}\right]}$$

where $\frac{(n-1)}{k \times int\left[\frac{N-m}{k}\right]}$ is normalization coefficient.

Stochastic signals are more fractal-like with a higher length $L(k)$ than periodic time series.

Sevcik Fractal Dimension (SFD). A method to estimate another FD from a set of N values in a one-dimensional signal between time 0 and t_{max} (Sevcik, 2010). The time series was subjected to a double linear transformation that maps it into a unit square. The normalized abscissa of the square is x_i^* and the normalized ordinate is y_i^*, both of them defined as

$$x_i^* = \frac{x_i}{x_{max}}$$
$$y_i^* = \frac{y_i - y_{min}}{y_{max} - y_{min}}$$

where x_{max} is the maximum x_i and y_{min} and y_{max} are the minimum and maximum y_i. The fractal dimension of the waveform (SFD) is then approximated by D as

$$\mathrm{SFD} \approx \mathrm{D} = 1 + \frac{\ln(L)}{\ln(2.N')}$$

where L is the length of the curve in the unit square and $N' = \mathrm{N} - 1$.

Spectral Entropy (SpEn). SpEn quantifies the spectral complexity of the EEG signal. If the EEG signal consists of a wide range of dominant frequencies, the SpEn will be high; otherwise, it will be low. As an example, white noise has higher SpEn than a sine wave because a sine wave is predictable and it has information. SpEn quantifies the regularity or randomness of the power spectrum during a period of time, and it can be used as a biomarker in studies (Tian et al., 2017). We use the entropy function in MATLAB 2020b to calculate spectral entropy. The equations for SpEn arise from the equations for the power spectrum and probability distribution for a signal. For a signal $x(n)$, the power spectrum is $S(m) = |X(m)|^2$, where $X(m)$ is the discrete Fourier transform of $x(n)$. The probability distribution $P(m)$ calculates as follows:

$$P(m) = \frac{S(m)}{\sum_i S(i)}$$

And the SpEn H follows as

$$H = -\sum_{m=1}^{N} \mathrm{P(m)}\ log_2 P(m)$$

***Approximate* Entropy (ApEn)**. ApEn is an index that denotes the regularity, complexity, and predictability of nonlinear time series, which quantifies the irregularity, and complexity of a signal. (Delgado-Bonal & Marshak, 2019).The ApEn of the perfectly regular time series like a sinusoidal signal is significantly smaller than the stochastic time series. So regular signal containing repetitive patterns has a relatively small value of ApEn, while the less predictable stochastic signal has a higher value of ApEn. A lower entropy value indicates predictability and high regularity of a signal. Conversely, a higher entropy value shows irregularity and lower self-similarity in a signal. In this research, the ApEn of the EEG signals was calculated. ApEn calculates from the correlation integral $C_i^m(r)$ related to the embedded signal in an m-dimensional space.

ApEn of signal with N data points x(1), x(2), . . ., x(N) is calculated as follows:

$$ApEn(m,r,N) = \frac{1}{N-m+1}\sum_{i=1}^{N-m-1} logC_i^m(r) - \frac{1}{N-m}\sum_{i=1}^{N-m} logC_i^{m+1}(r)$$

where, $C^m(r)$ is the probability that two sequences will match for m points, and $C^{m+1}(r)$ is the probability that two sequences will match for m+1 points. In this research, m is set to 2 and r is set to 0.20% of each signal variance.

Phase* Am*plitude* Co*upling (PAC). We calculate PAC by direct PAC estimator (dPAC; Özkurt & Schnitzler, 2011). Let $\boldsymbol{a_H(n)}$ be the amplitudes of high-frequency oscillation $\boldsymbol{z_H(n)}$ and also $\boldsymbol{\varphi_L(n)}$ the phase of low-frequency oscillation $\boldsymbol{z_L(n)}$, where $\boldsymbol{z_L}$ and $\boldsymbol{z_H}$ are bandpass filtered complex form representations from two frequency band signals such that

$$\boldsymbol{z_L(n) = |z_L(n)|e^{i\varphi_L(n)}} \quad , \quad \boldsymbol{a_L = |z_L(n)|}$$
$$\boldsymbol{z_H(n) = |z_H(n)|e^{i\varphi_H(n)}} \quad , \quad \boldsymbol{a_H = |z_H(n)|}$$

$$\boldsymbol{dPAC = \frac{1}{\sqrt{N}} \frac{|\sum_{n=1}^{N} a_H(n)e^{i\varphi_L(n)}|}{\sqrt{\sum_{n=1}^{N} a_H(n)^2}}}$$

The low- and high-frequency oscillations are obtained by bandpass filtering the signal $s(t)$ in delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30) and gamma (30–60 Hz).

Statistical Analysis. All analyses were made using MATLAB software. The normality assessment was done using the Shapiro-Wilk test. Since the null hypothesis of normality could not be rejected, a parametric paired *t*-test was performed to assess the significance of the difference between the pretreatment and posttreatment aphasia group, while an unpaired *t*-test was used for analyzing differences between aphasia and control groups.

Clinical Assessments

The behavioral analysis included the Persian version of the aphasia battery (Nilipour et al., 2016), the forward and backward digit/word/nonword span (Conway et al., 2005), and the Stroop test (Siegrist, 1997), which were acquired at baseline and the final LZNFB session for the aphasic group. Each exam contained multiple questions. For each subtest, the Shapiro-Wilk test was used to examine the normality of the data. For normal and nonnormal distributions, the paired *t*-test (T) or Wilcoxon (Z) was subsequently used. * indicates significant changes ($p < .05$) in Table 3.

Statistical assessments were made with parametric *t*-test and nonparametric Wilcoxon signed ranked test for data showing normal and nonnormal distribution respectively.

Results

Our results involved both clinical and EEG assessments, which are described as the following.

Results Derived From Clinical Assessments

Clinical assessments were applied just for the experimental aphasic group to show the clinical recovery over the LZNFB treatment. Our clinical assessments showed improvement in language, working memory, and attention scores in aphasic patients after treatment (Table 2). Significant changes ($p < .05$) were starred.

Results Derived From EEG Metrics

In our EEG analysis, we estimated complexity and PAC in three groups including pretreatment aphasic, post-treatment aphasic, and nonaphasic control group. Then we compared the results to see whether LZNFB helped to normalize EEG disruption in aphasia.

Complexity

A remarkable change in EEG complexity was observed in association with LZNFB treatment. Complexity analysis were performed by Katz, Higuchi, and Sevcik fractal dimension methods as well as SpEn and ApEn in three groups. We differentiated the left and right hemispheres in our analysis and found more dominant differences in the left rather than the right hemisphere. Table 3, Figure 1 shows EEG complexity in three groups in the left hemisphere. Significant differences ($p < .05$) were observed between pretreatment and two other groups (pretreatment and posttreatment, pretreatment and normal). No significant differences were observed between the posttreatment aphasic group and nonaphasic group. That means posttreatment aphasic complexity gets much close to the nonaphasic control group. Significant changes were shown by * for $p < .05$) and ** for $p < .01$.

Table 2

Systolic and Diastolic Blood Pressure Changes (Postingestion – Preingestion)

Behavioral test	Subtest	Pretreatment (mean)	Posttreatment (mean)	*p*
Language	Auditory perception	171	182	.028*
	Lexical richness	0.75	0.863	.011*
	Speed	34.27	52.25	.003*
	Repeat	80.30	94.30	.003*
	Utterance	8.23	12.30	.003*
Working memory	Forward digit	6.15	8.84	.004*
	Forward word	5.15	6.46	.003*
	Forward nonword	3.15	4.53	.002*
	Backward digit	2.30	5	.000*
	Backward word	2.84	4.92	.000*
	Backward nonword	0.92	1.69	.000*
Attention	Congruent error	3.92	1.53	.166
	Incongruent error	11	2.23	.003*
	Congruent correct	31.46	38.46	.004*
	Incongruent correct	21	36	.002*

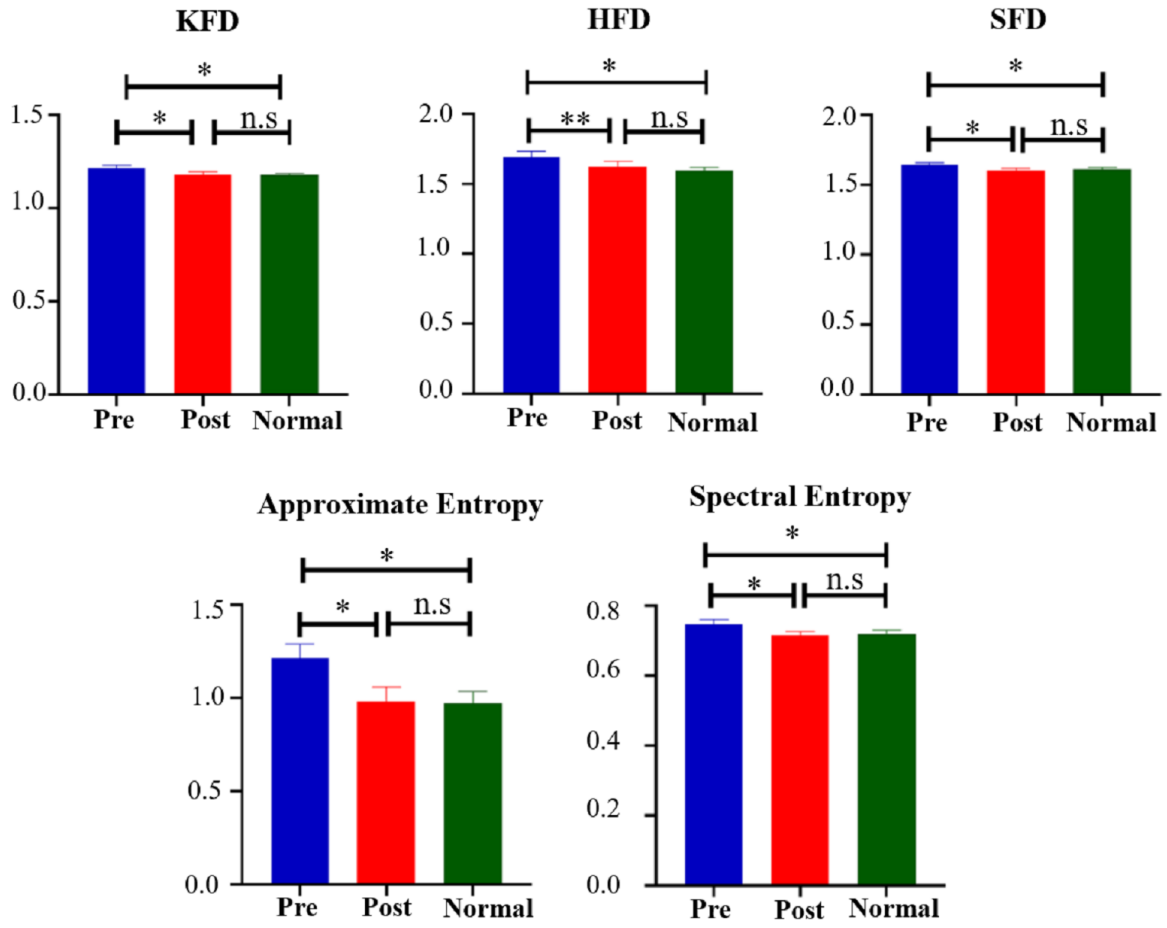
Table 3

EEG Complexity Analysis in Three Groups at the Left Hemisphere

Left	Pretreatment		Posttreatment		Control		*p*		
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Pre vs. Post	Pre vs. Control	Post vs. Control
KFD	1.212	0.067	1.177	0.069	1.170	0.037	.040*	.0500	.9000
HFD	1.692	0.133	1.623	0.119	1.599	0.067	.009**	.0422*	.7381
SFD	1.646	0.041	1.604	0.046	1.609	0.042	.002**	.0500	.7861
SpEn	0.749	0.040	0.716	0.035	0.715	0.040	.001**	.0407*	.5369
ApEn	1.212	0.256	0.983	0.249	0.974	0.235	.005**	.0217*	.9299

Pre: pretreatment group; Post: posttreatment group; *SD*: standard deviation; SpEn: spectral entropy; ApEn: approximate entropy.

Figure 1. *EEG Complexity Analysis in Three Groups at the Left Hemisphere.*



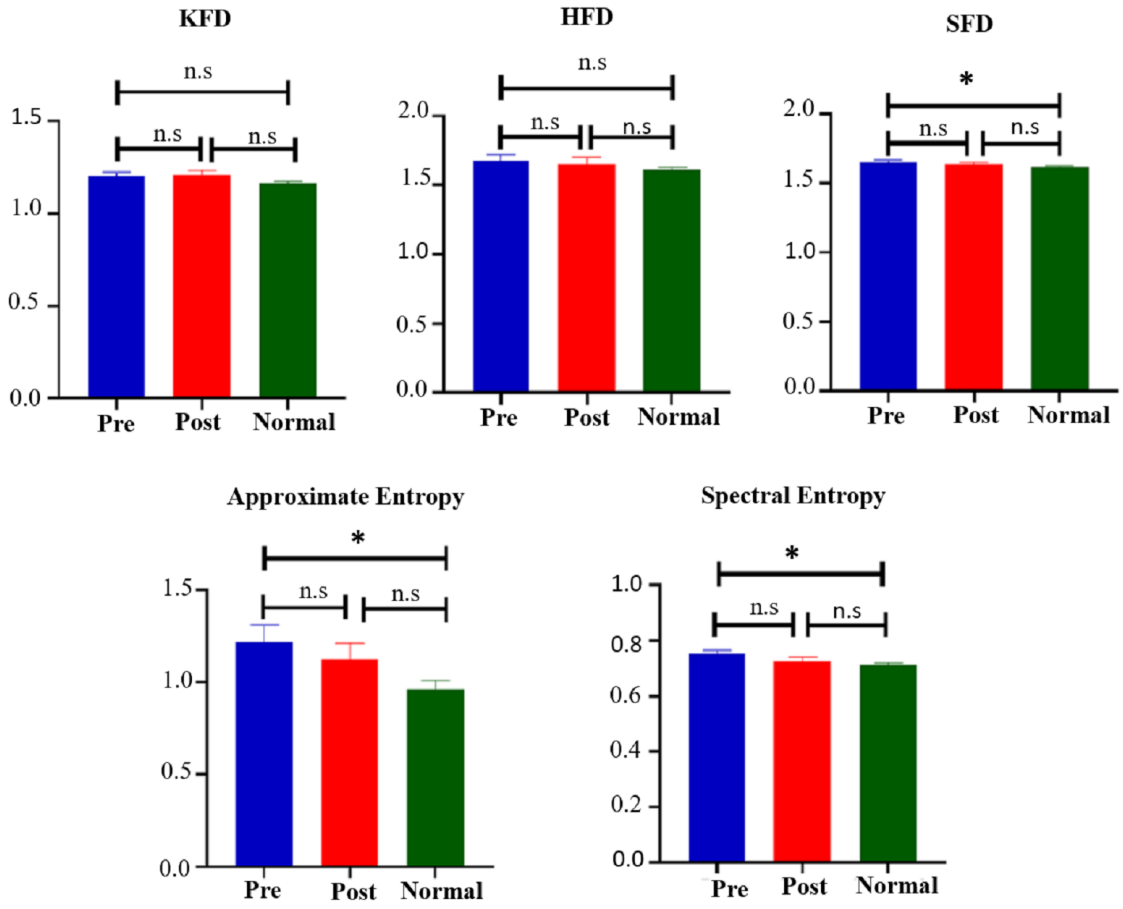
In the right hemisphere, KFD and HFD values were not significantly different between groups. However, SFD, Approximate Entropy, and Spectral Entropy showed significant differences between pretreatment aphasic and nonaphasic groups. No significant differences were observed between pretreatment and posttreatment aphasic groups and between posttreatment aphasic and nonaphasic groups (Table 4, Figure 2).

Table 4

EEG Complexity Analysis in Three Groups at the Right Hemisphere

Right	Pretreatment		Posttreatment		Control		*p*		
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Pre vs. Post	Pre vs. Control	Post vs. Control
KFD	1.202	0.074	1.209	0.079	1.165	0.035	.698	.0902	.0554
HFD	1.674	0.156	1.651	0.167	1.608	0.086	.736	.1692	.3836
SFD	1.651	0.045	1.635	0.049	1.616	0.030	.398	.0203*	.2272
SpEn	0.750	0.051	0.726	0.052	0.713	0.029	.150	.0237*	.4003
ApEn	1.216	0.328	1.124	0.305	0.963	0.191	.306	.0161*	.0974

Figure 2. *EEG Complexity in Three Groups at the Right Hemisphere.*



Phase-Amplitude Coupling (PAC)

We estimated theta-gamma PAC in groups and compared the results. Significant changes have been shown in Table 5. The most significant change between the pretreatment and the posttreatment group was observed at Fp2-C4 (p = .0083), Cz-Fp1 (p = .0155), and Cz-F3 (p = .0175). Pretreatment versus control groups showed the most significant difference at C3-Fp2 (p = .0009), Fp1-O2 (p = .0084), and Fp1-T6 (p = .0132) and posttreatment versus control group showed the most significant change at C3-Fp2 (p = .0024), Cz-Fp1 (p = .0047), T5-F4 (p = .0057).

Figure 3. *Theta-Gamma PAC in Pre-Treatment, Post-Treatment, and Normal Group.*

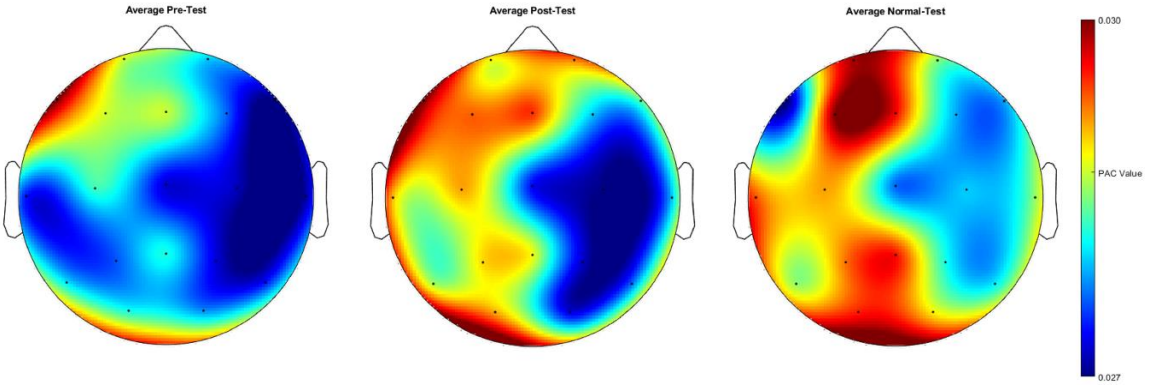


Table 5

EEG Complexity Analysis in Three Groups at the Right Hemisphere

Pretreatment vs. Posttreatment			Pretreatment vs. Control			Posttreatment vs. Control		
Amplitude channel	Phase channel	*p*	Amplitude channel	Phase channel	*p*	Amplitude channel	Phase channel	*p*
Cz	Fp1	**.0155**	F3	Fp2	.0150	Fz	Fp1	.0126
F4	F3	.0229	C3	Fp2	**.0009**	F4	Fp1	.0098
Cz	F3	**.0175**	Fp1	F4	.0376	C3	Fp1	.0458
F4	Fz	.0457	Fp2	F4	.0270	Cz	Fp1	**.0047**
Fp2	F4	.0301	T5	F4	.0386	C3	Fp2	**.0024**
Fp2	Cz	.0445	Fp1	Cz	.0381	F4	F3	.0460
Fp2	C4	**.0083**	Pz	Cz	.0429	T5	F4	**.0057**
Fp2	P4	.0427	O1	Cz	.0380	T5	F8	.0099
Fp1	O2	.0278	Fp1	C4	.0476	P4	C4	.0369
F3	O2	.0321	F8	T4	.0466	Fz	T4	.0125
---	---	---	Fp1	P4	.0380	T4	T4	.0428
---	---	---	Fp1	T6	**.0132**	T5	T4	.0242
---	---	---	Fp1	O2	**.0084**	P3	T4	.0259
---	---	---	---	---	---	F7	P4	.0446
---	---	---	---	---	---	T3	P4	.0408
---	---	---	---	---	---	C4	P4	.0405
---	---	---	---	---	---	F3	O2	.0245
---	---	---	---	---	---	T3	O2	.0146

Discussion

In aphasia, cognitive performance becomes poor and the organization of the brain network architecture is affected. In this study, we aimed to show EEG disruptions in aphasia and the possible effect of LZNFB on improving EEG abnormalities and clinical symptoms. Therefore, we used behavioral and EEG assessments at baseline and after 15 sessions of LZNFB. Our behavioral assessments showed improvement in language, working memory, and attention scores in our aphasic group after LZNFB and implied as decreased aphasia symptoms. Our EEG findings were congruent with clinical improvement and showed that complexity, PAC, and coherency changed to a normal level after treatment. We think that this study may pave the way to provide biomarkers for treatment targets in chronic aphasia.

Complexity

In this study, we reported NFB-induced changes in the EEG complexity in aphasia. In fact, the brain is a complex nonlinear system, and the EEG signal is demonstrated nonlinearity at the neuronal level. Therefore, it would be appropriate to use nonlinear methods to analyze EEG signals (Klonowski, 2009). Moreover, a nonlinear dynamic approach could provide novel insights into brain diseases and could be a useful tool in understanding the mechanisms of neuronal plasticity after injury and during rehabilitation (Sun et al., 2017).

Brain damage can result in dysfunction of particular parts of the brain and can be reflected in the complex dynamics of its neural activity (McBride et al., 2014), loss of synaptic connections, and neurotransmitter deficiency (Sun et al., 2017). Therefore, we hypothesized that the complexity of

the experimental group would be improved with training and decrease to a normal level.

According to Figure 1, the complexity in the pretreatment group was the most among the groups, but it decreased over the LZNFB. So posttreatment aphasic complexity was much closer to the nonaphasic group. We estimated complexity in the left and right hemispheres separately and found more dominant differences in the left rather than right hemisphere, which is in line with the study of Wu et al. (2015). At left hemisphere, KFD, HFD, SFD, ApEn, and SpEn showed that complexity in the aphasia group at baseline was significantly different from that of in posttreatment aphasia and nonaphasic control group. However, the differences between groups in the right hemisphere were less significant. Considering the fact that the experimental group had an injury in the left hemisphere and this hemisphere plays a great role in language performances, EEG signal alteration in this hemisphere may add support for the effectiveness of LZNFB treatment and decreased EEG complexity can be implied as clinical improvement. In line with our findings, several studies associated decreased complexity with improvement. For example, decreased complexity after recovery has been reported in depression (Okazaki et al., 2013) and autism (Okazaki et al., 2015). Nevertheless, our findings are opposed to the study of Sun et al. (2017), showing increased complexity in the contralesional hemisphere after treatment in stroke patients (Sun et al., 2017). To clear up these diversities in results, several factors such as lesion size, affected hemisphere, and postonset should be taken into account. If the affected region of the brain is large, there might be insufficient cortical tissue left in the ipsilesional hemisphere. Therefore, the right hemisphere is more probable to activate in order to help the defiant and weakened left hemisphere. Our participants had the right hand affected, suggesting a lesion in the left hemisphere. Moreover, our participants were in the chronic phase and their EEG data were assessed at least 7 months after brain damage (Table 1). By showing decreased complexity to normal levels over the LZNFB treatment we provide evidence of the potential of using complexity as an indicator of improvement in aphasia.

PAC

With the present study, we showed significant differences in theta-gamma coupling after treatment (Table 5, Figure 3). Our findings provide evidence that LZNFB can enhance PAC in aphasic patients to a normal level. This enhancement was found over various cortical sites, especially in the left hemisphere. It is necessary to consider that the human brain is unlikely to be a composition of neatly separated neural modules whose oscillatory signatures can be manipulated independently from each other. Rather, its essence lies in a myriad of dynamic neural interactions that serve the integration of information across various temporal and spatial processing scales (Tononi, 2010). One promising mechanism for how such integration may be implemented in the brain is through a nested hierarchy of neural oscillations (Lakatos et al., 2005). Studies have shown that the phase of oscillations arising from slower global computations can flexibly modulate the amplitude of faster local oscillations (Bonnefond & Jensen, 2015). As oscillations in the human brain are known to interact within nested hierarchies via PAC, and PAC increment has been reported in neuromodulation techniques (Helfrich et al., 2016; Noda et al., 2017), we expected NFB might also be able to increase the macroscopic detectability of such coupling.

Increased PAC in our study, over the LZNFB, has two major implications. On the one hand, it implies improved cognitive performance in aphasia. Our findings were in line with previous studies showing the association between PAC and visual perception (Händel & Haarmeier, 2009), feedback processing (Cohen et al., 2008), memory recall (Tort et al., 2009), and visual (Okazaki et al., 2013) and motor mapping (Tzvi et al., 2016). Similarly, the association between increased PAC coupling with improved task performance was reported (Vivekananda et al., 2021).

On the other hand, increased PAC in our study is relevant for language performance in aphasia. In fact, theta-gamma cross-frequency coupling in the left hemisphere has been proposed to subserve the concatenation of phonemes to syllables (Canolty et al., 2006), and it adopts to speech rate (Lizarazu et al., 2019). Notably, the increase in PAC could not have been due to an increase in the number of neurons, as lost neurons cannot be regenerated during rehabilitation training. However, following the neuronal death, spared neural structures in adjacent tissue, and remote structures in the ipsileisional and contralateral hemispheres, undergo significant functional changes.

Previous studies also associated dysfunction in PAC with several clinical conditions such as Parkinson's disease (de Hemptinne et al., 2013), autism spectrum disorder (Khan et al., 2013), and epilepsy (Edakawa et al., 2016). Here, by demonstrating

enhanced theta-gamma PAC to normal levels over the NFB treatment, we provide evidence in potential of using PAC as an indicator of improvement in aphasia.

Taken together, by demonstrating enhanced theta-gamma PAC and decreased complexity to normal levels over the LZNFB treatment, we provide evidence of the potential of using PAC, and complexity as an indicator of improvement in aphasia. We have shown here the ability of LZNFB to be used as a neuromodulatory tool in decreasing symptoms and EEG disturbances in aphasia. Our finding of NFB efficacy in aphasia is supported by previous case studies (Mroczkowska et al., 2014; Rozelle & Budzynski, 1995).

Limitations

There were some limitations in this study. First, the data were collected from aphasic subjects in the chronic phase with homogenous lesion locations and clinical impairment, which could limit the generalization of our findings to other variations in aphasia. Small sample size is another limitation of our study. Future studies that evaluate a greater number of patients and healthy subjects will be necessary to verify the conclusions of the present study.

Conclusions

We conclude that LZNFB treatment was effective in decreasing EEG disturbances and symptoms in aphasia. We think that our findings in complexity and PAC could provide important insights into the electrophysiological profile in aphasia and its alterations after treatment.

Author Disclosure

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