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Rereferencing of clinical EEGs with nonunipolar mastoid reference to infinity reference by REST

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HIGHLIGHTS

- REST was introduced and assessed to transform nonunipolar mastoid reference to an infinity reference.
- It produced small absolute errors and high correlations between the computed infinity reference and the true one.
- It is an effective and robust resolution for those nonunipolar clinical EEGs.

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ABSTRACT

Objective: Conventional electroencephalography (EEG) offline subtraction rereferencing is invalid for many clinical practices when adopting a specific nonunipolar recording montage (e.g., the ipsilateral mastoid (IM) and contralateral mastoid (CM)). Further comparative analyses would thus be blocked due to the lack of a uniform offline reference. Therefore, our goal was to resolve this problem by introducing and assessing the reference electrode standardization technique (REST) to transform nonunipolar mastoid montages into a computational zero reference at infinity (IR) offline.
Methods: For EEG signals and power/connectivity configurations, simulation and clinical schizophrenia resting-state EEG datasets were used to investigate the performance of REST.
Results: REST produced small absolute errors (signal level: 1.21–1.26; power: 0.0057–0.021; connectivity: 0.066–0.088) and high correlations (>0.9) between the IM/CM-IR and true IR references. Using clinical data with the IM online reference, REST revealed valuable changes in spectral and connectivity ($P < 0.05$) in schizophrenia patients, consistent with previous studies.
Conclusions: These results demonstrated that REST transformation could be adopted to resolve the offline rereferencing of clinical EEGs with specific nonunipolar mastoid references.
Significance: REST could be an effective and robust resolution for nonunipolar clinical EEGs and could therefore retrieve these data for further analysis by deriving a favorable offline reference IR.

1. Introduction

The derivation of electroencephalography (EEG) is generally from the potential difference between the "active" electrode of interest and a reference point (Osselton, 1965), which is theoretically supposed to be located at infinity (i.e., a "true" zero potential). In addition, it is practically set at a specific body site, such as an assumed neutral location (like the nose, ear, mastoid, chin, knee and ankle, etc.), a consecutive neighborhood point (such as a sphenoid bone montage, etc.), or a locus convenient for electrode positioning (e.g., Cz and Fz) (Lehmann et al., 1998), usually varying with the needs of individual EEG experimenters (Rosenfeld, 2000). To ensure internal validity and across-study comparability among different recording schemes, rereferencing strategies have been indispensable for EEG offline analyses

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(Kayser and Tenke, 2010, Mercier et al., 2017, Yao, 2001, Yao et al., 2019).

For unipolar montages that only set one common referencing point for all electrodes, a desired offline reference, such as the averaged reference (AR) or the linked-ear reference (LM), could be easily obtained by deducting the specified rereferencing signal from each channel to replace the original recording reference. However, this offline conventional subtraction would be invalid in many clinical cases in which the monitoring of pathological EEG activities must be performed with a specific nonunipolar mastoid montage (maybe not a uniform reference), such as the contralateral mastoid (CM) or the ipsilateral mastoid (IM) (Mercier et al., 2017, Michelmann et al., 2018). Because more than one independent recording reference is implied in the dataset, it cannot be replaced simultaneously by any linear transform (Liu et al., 2015). Without access to a uniform offline reference, further comparative analyses, as well as large clinical EEG applications, are thus limited, and few related investigations can be found, although many such clinical data have been collected in practice.

This work attempted to solve this problem by introducing the reference electrode standardization technique (REST) (Dong et al., 2017, Yao, 2001) for such nonunipolar mastoid montages to derive a computational zero reference at infinity (IR), and it investigated the performance of REST on these nonunipolar mastoid referenced clinical EEGs offline. As a novel method that approximately converts an average or unipolar reference into a zero reference (Dong et al., 2017, Yao, 2001), REST has been increasingly acknowledged by EEG/ERP research groups worldwide (Yao et al., 2019). By using REST for standardization of reference, it could be essential to release these clinical EEGs from limited offline explorations. Note that, compared with other common reference schemes (such as Cz, LM and AR, etc.), the IR reference could provide many consistent or even more favorable results in EEG offline analyses, such as ERP topographies (Dong et al., 2019, Liu et al., 2015, Qin et al., 2017, Tian and Yao, 2013, Yao et al., 2007), EEG spectra (Chella et al., 2017, Yao et al., 2005), and EEG networks (Chella et al., 2016, Marzetti et al., 2007, Qin et al., 2010). However, the reformation of nonunipolar mastoid montages has not yet been reported. This study is the first to transfer these offline nonunipolar mastoid schemes using REST and detect the feasibility with practical EEG data, as is expected to facilitate offline explorations of these specific clinical EEGs.

In our work, the performance of REST was first quantified based on a simulation dataset generated from a real resting-state EEG dataset. Indices including absolute error, relative error and Pearson's correlations between the IR signals (IR transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar reference by REST) were calculated. Next, the power spectrum and network connectivity, the most conventional cut-in points for EEG studies, were estimated to compare the corresponding indices between them. Then, a clinical schizophrenia EEG dataset with a montage of ipsilateral mastoid (IM) was investigated to test the feasibility of REST in practical studies.

2. Methods

2.1. Data collection

Dataset 1 of laboratory EEGs was gathered from 41 healthy subjects (32 men/9 women, mean age 23.9 ± 1.6 years old) and recorded using a 62-channel EEG system (Brain Products GmbH, Gilching, Germany) with a FCz montage. The channel locations of 62 channels are showed in Fig. 1. EEG dataset 2 was online bandpass filtered (0.01–100 Hz). The clinical EEGs were collected in the Fourth People's Hospital of Chengdu from a 16-channel (FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8) Neuro01 system (Weisi Medical Technology Inc., Nanjing, China) with a montage of ipsilateral mastoids (IMs). The dataset 2 contained two groups consisting of 21 schizophrenia patients and 21 healthy controls, with matched controls by age and gender (11 men, aged 25 ± 3.2 years old; 10 women, aged 25 ± 3.2 years old).

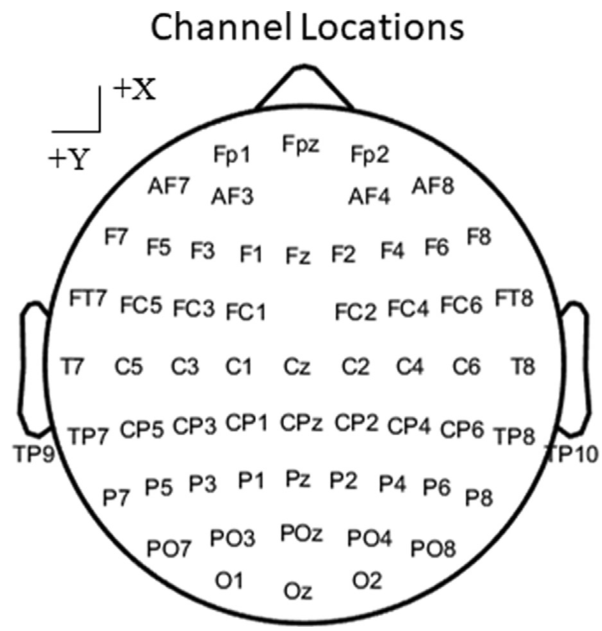

Fig. 1. Channel locations of EEG recordings.

Both experiments were approved by the Ethics Committee of Life Science and Technology of University of Electronic Science and Technology of China (UESTC). Each participant provided written consent and was given oral instruction before the recording of a 5-minute resting state with the eyes closed. All electrodes were arranged on the scalp according to the extended international 10–20 system. The scalp was cleaned to ensure good contact with the electrode and a lower impedance of less than 5 kΩ.

Both datasets were sampled online with a frequency of 500 Hz. A quality assessment (QA) tool from the WeBrain platform (https://webrain.uestc.edu.cn/) (Dong et al., 2021) was used to detect and reject bad blocks with different types of artifacts. The main QA processing contains: 1) EEG signals were high-pass filtered (>1 Hz) to remove linear drift first; 2) continuous EEG data were segmented as a mass of windows; 3) bad data in small windows of each channel were detected by 4 methods (detecting constant or NaN/Inf signals, unusually high or low amplitudes, high or power frequency noises, and low correlation signals); and 4) a number of data quality masks were generated and used to obtain continuous good data blocks. Next, continuous EEG raw data were offline filtered with a bandpass of 1–40 Hz, and further analyses were conducted on uncontaminated epochs of clean data with a length of 5 s.

2.2. Reference electrode standardization technique (REST) and its implementation

The reference electrode standardization technique (REST) was developed from a distributed source model (Dong et al., 2017, Yao, 2001, Yao et al., 2005), in which the potential V (N channels $\times$ T time points) on the scalp is assumed to be generated from the function of a lead-field matrix G (N channels $\times$ M sources) and an active source S (M sources $\times$ T time points). Here, G expresses the forward model theoretically computed with the infinity reference.

$$V = \begin{bmatrix} v_1^1 & \cdots & v_T^1 \\ \vdots & \ddots & \vdots \\ v_1^N & \cdots & v_T^N \end{bmatrix} = GS \tag{1}$$

where v_i^j, $1 \leq j \leq N$, $1 \leq i \leq T$ is a sample at the ith time point and jth channel. Similarly, the scalp EEG potential referenced to ipsilateral matroid V_{IM} (of size N-2 channels $\times$ T time points) can be expressed as:

$$V_{IM} = V - \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \\ 0 & 1 \end{bmatrix} \begin{bmatrix} v_1^{m1} & \cdots & v_T^{m1} \\ v_1^{m2} & \cdots & v_T^{m2} \end{bmatrix}$$
$$= GS - wl_{IM}S = (G - wl_{IM})S = G_{IM}S \tag{2}$$

where w is a matrix (N channels $\times$ 2) with each of its elements being 1 or 0; l_{IM} is the matrix ($2 \times M$ sources) in G corresponding to the reference channels (i.e. ipsilateral matroids); v_i^j, $j = m1$ *or* $m2$, $1 \leq i \leq T$ is a sample at the ith time point and $m1/m2$ channel. G_{IM} is the lead-field matrix for the recording reference of IM and depends on the head model, source configuration and electrode montage, similar to the situation of G.

Then, the distribution of S can be derived with the minimum norm solution (MNS) and substituted into the equation of V to reconstruct the scalp potential, referenced at infinity,

$$V = GS \approx G\tilde{S} = G(G_{IM}^{+}V_{IM}) = (GG_{IM}^{+})V_{IM} \tag{3}$$

where G_{IM}^{+} denotes the Moore-Penrose generalized inverse of the matrix G_{IM}; and V_{IM} is the scalp EEG recordings with ipsilateral matroid reference (see the details of the REST algorithm in Yao et al. (Dong et al., 2017, Yao, 2001, Yao et al., 2005) and download the tool (EEGLABPluginVersion-REST_v1.2_20200818) at http://www.neuro.uestc.edu.cn/name/shopwap/do/index/content/96 for free).

Similarly, recordings with other references V_R, such as linked mastoids or common average, etc. (Dien, 1998, Hagemann et al., 2001), could also be transformed into the neutral infinite reference by the equation above only if the lead field matrix corresponding to the chosen reference is available.

$$V = GS \approx (GG_{R}^{+})V_R \tag{4}$$

where G_R^{+} denotes the Moore-Penrose generalized inverse of the matrix G_R; G_R is the lead-field matrix for the average reference and depends on the head model, source configuration and electrode montage, similar to the situation of G; V_R is the scalp EEG potential referenced to average.

2.3. Method assessment

To assess the performance of REST rereferencing in EEG analysis, simulations were assumed using dataset 1. First, the IM/CM referenced data were generated from the data with a montage of FCz (by subtracting TP9 or TP10 and then deleting TP9 and TP10). Next, the REST method can convert an average or unipolar reference into a zero reference at infinity (IR) (Dong et al., 2017, Yao, 2001, Yao et al., 2019). Performances of the REST were quantified using the mean absolute error, relative error and Pearson's correlations between the IR signals (IR transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references by REST). Furthermore, the power spectrum and network connectivity, the most conventional cut-in points for EEG studies, were estimated to compare the corresponding indices between them. Using the EEG tools on the WeBrain platform (https://webrain.uestc.edu.cn/) (Dong et al., 2021), the relative power (power of specific band/total power across full band 1–40 Hz) of each channel was evaluated by time–frequency analysis with fast-Fourier transform (FFT), and the connectivity coefficients between each pair of sensors were estimated with the phase synchronization index (PSI). Each analysis was performed separately in typical EEG frequency bands (delta: 1–4 Hz, theta: 4–8 Hz, alpha: 8–12.5 Hz, beta: 12.5–30 Hz, gamma: 30–40 Hz). Subsequently, the performances of the REST were quantified by the mean absolute error, relative error and spatial Pearson's correlations between the indices with different IR rereferences derived by REST on IM/CM and unipolar (FCz) references to test the robustness of REST transformation in various situations. In addition, errors and spatial correlations between different AR rereferences derived by REST were also calculated.

Finally, REST was further applied to clinical EEGs with a recording reference of IM, consisting of two groups of schizophrenia patients and healthy controls, to obtain the corresponding IR and AR references to test the feasibility of REST in practical studies. The comparisons of power and networks between schizophrenia and controls were conducted in IR and the original recording reference IM. To follow normal distributions, Fisher's z-scores of connectivity coefficients and relative power indices were calculated first. And then, two sample t-tests were used to test the difference in power/connectivity between schizophrenia patients and controls.

3. Results

3.1. Results at the signal level

To quantify the performances of the REST method, the absolute error, relative absolute error and correlation (R) between the IM/CM-IR signals (IR transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references) were calculated. The transformed IR signals (IM-IR and CM-IR) from an example subject can be seen in Fig. 2A, and the mean results across subjects are shown in Fig. 2B. For IR signals, REST resulted in approximately 1.2655/1.2177 (IM/CM) mean absolute errors (with standard errors 0.065/0.028), 0.3199/0.3056 (IM/CM) mean relative errors (with standard errors 0.015/0.009), and 0.9283/0.9347 (IM/CM) mean correlations (with standard errors 0.011/0.005). In addition, the results of errors between different AR rereferences derived by REST are shown in Figures S1-S2.

3.2. Results of power indices and networks

To quantify the performance of the REST method, the relative power indices from the IM/CM-IR signals (IR transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references by REST) were calculated. The mean results across subjects are shown in Fig. 3, showing that REST in resulted power indices similar to the true ones. In Fig. 4, the results of the mean absolute and relative errors between the relative powers obtained from the IR signals (transformed from nonunipolar IM/CM references by REST) and the true IR signals (transformed from unipolar references) are shown. For relative power indices in the delta, theta, alpha, beta and gamma bands obtained from IR signals, REST resulted in approximately 0.028, 0.0073, 0.021, 0.012 and 0.0057 mean absolute errors (with standard errors 0.0045, 0.001, 0.0033, 0.0022 and 0.0012) and 0.10, 0.056, 0.062, 0.075 and 0.19 mean relative errors (with standard errors 0.016, 0.008, 0.009, 0.012 and 0.036), respectively.

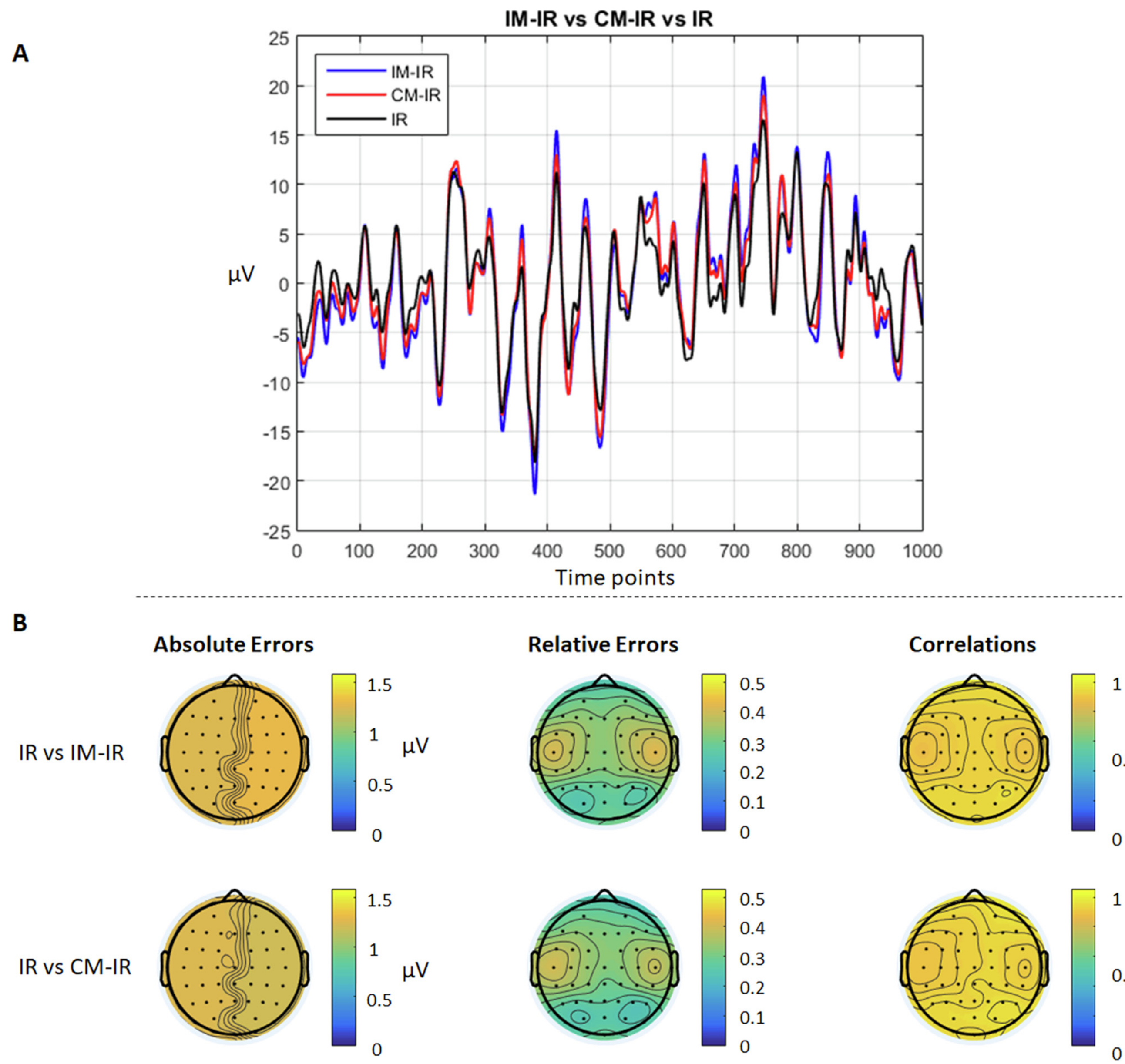

Fig. 2. Results at the signal level. A: IR signals (FC3, from an example subject) transformed from non-unipolar IM (IM-IR) and CM (CM-IR) references by REST and the true IR signals transformed from unipolar reference by REST. B: Results of mean errors and Pearson's correlations between the IR signals transformed from nonunipolar mastoid references by REST and the true IR signals (transformed from unipolar references). IR: infinity reference; IM: ipsilateral mastoid; CM: contralateral mastoid; REST: reference electrode standardization technique.

Fig. 5 shows that the EEG connectivities in the delta, theta, alpha, beta and gamma bands obtained from REST-transformed IR signals (transformed from nonunipolar IM/CM references) are similar to the connectivities obtained from true IR signals (transformed from unipolar references). In Fig. 6, the results of mean absolute and relative errors between them are shown. For connectivities in the delta, theta, alpha, beta and gamma bands obtained from IR signals, REST resulted in approximately 0.082, 0.07, 0.071, 0.066 and 0.088 mean absolute errors (with standard errors 0.01, 0.008, 0.009, 0.008, 0.012 and 0.008) and 0.19, 0.2, 0.14, 0.22 and 0.36 mean relative errors (with standard errors 0.025, 0.024, 0.019, 0.031, 0.056 and 0.026), respectively. In Fig. 7, the mean spatial Pearson's correlations across subjects between power indices/connectivities obtained from the IR signals (transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references) are shown, and correlations between them are all greater than 0.9. In addition, the results of errors and spatial correlations between power indices/connectivities from the AR signals (transformed from nonunipolar mastoid references by REST) and the true AR signals are shown in Figures S3-S7.

3.3. Application of REST in clinical EEG with a recording reference of IM

Finally, REST was applied to clinical EEGs with a recording reference of the ipsilateral mastoid (IM) to detect the characteristics of schizophrenia patients compared to healthy controls. The recording reference of IM was transformed to the computational zero reference at infinity (IM-IR).

The power and connectivity for each of the references, i.e., the original recording reference IM and the derived IR (IM-IR), were estimated for each frequency band. Student's t test was then

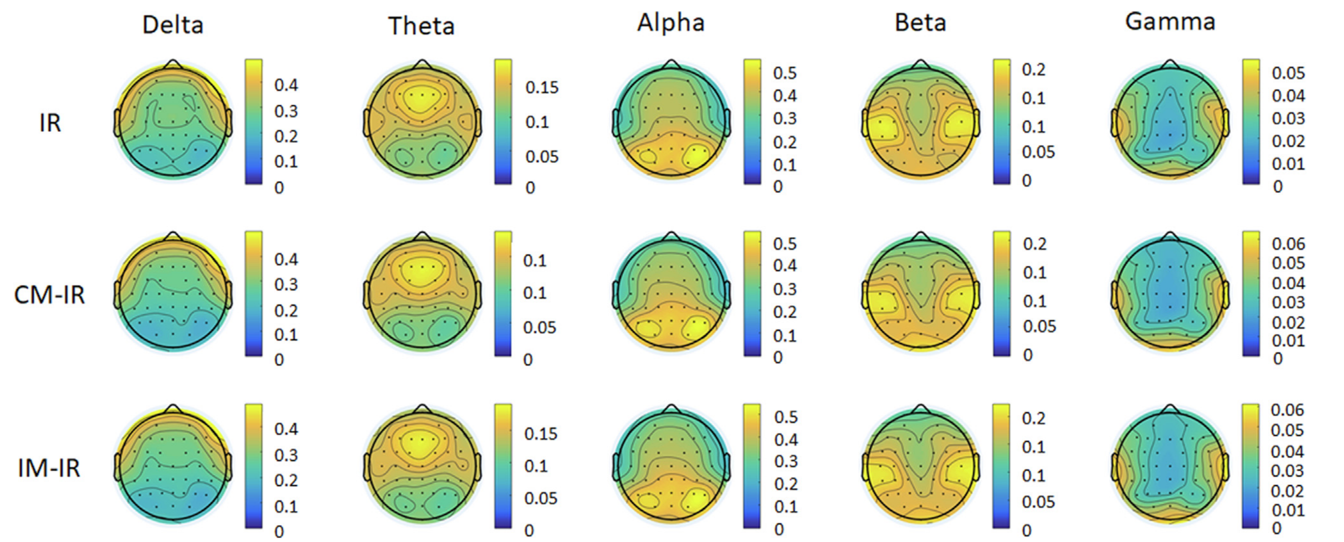

Fig. 3. Topographies of mean relative powers across subjects obtained from the IR signals (transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references). IR: infinity reference; IM: ipsilateral mastoid; CM: contralateral mastoid; REST: reference electrode standardization technique.

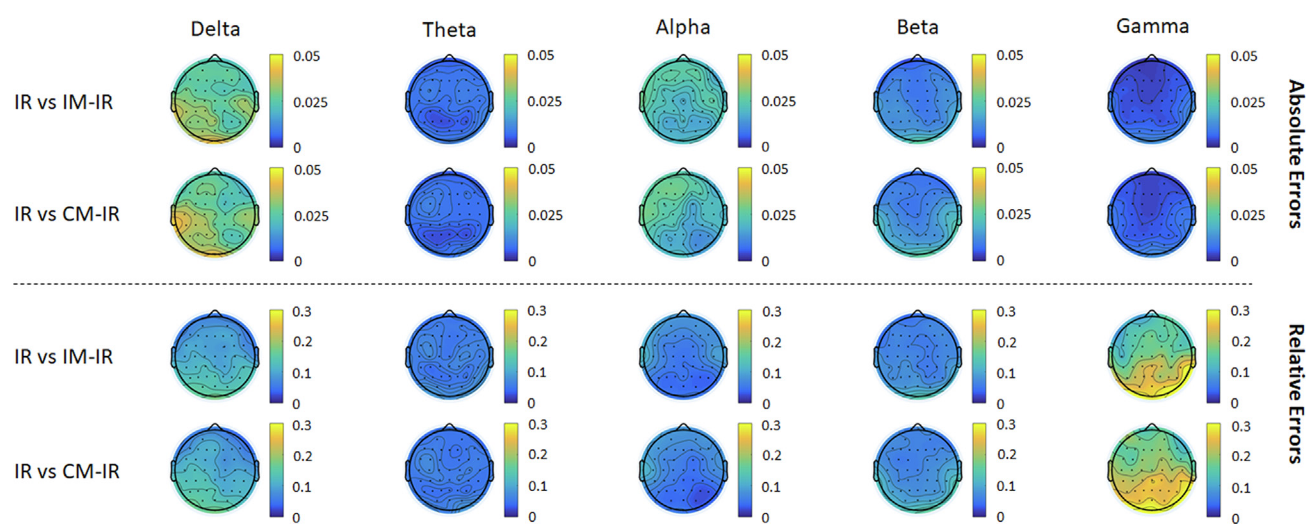

Fig. 4. Results of mean absolute and relative errors between relative powers obtained from the IR signals (transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references). IR: infinity reference; IM: ipsilateral mastoid; CM: contralateral mastoid; REST: reference electrode standardization technique.

conducted between the schizophrenia patients and controls. The statistical configurations corresponding to t values ($P < 0.05$) are shown in Fig. 8, revealing that, when in the IM-IR reference, the power for the schizophrenia group had a reduction in the alpha band (located in the frontoparietal area) and increases in the beta (located in the parietal, frontal and temporal areas) and gamma (located in the right frontal area) bands. In the IM reference, the power for the schizophrenia group had a reduction in the alpha band (located in the frontoparietal area) and increases in the beta (located in the parietal, frontal and temporal areas) and gamma (located in the left parietal, right temporal and frontal areas) bands. Fig. 8 also demonstrates that, when in the IM-IR reference, the connectivity for the schizophrenia group mainly showed a decrease in the delta (bilateral occipital-partial connections), theta (bilateral occipital-partial connections) and alpha (mainly frontoparietal and occipital-partial connections) bands and increases in the beta (few partial connections) and gamma (right frontoparietal connections) bands. In the IM reference, the connectivity for the schizophrenia group mainly showed a decrease in the delta (left occipital-partial connections) and theta (bilateral occipital-partial connections) bands and increases in the theta (bilateral temporal-partial connections) and gamma (bilateral temporal-partial connections) bands.

4. Discussion

This work focused on whether the reference electrode standardization technique (REST) could transform the clinical nonunipolar mastoid references into a computational zero reference at infinity and to release these special clinical EEGs for further processing. The comparison of configuration similarities in signal, power and connectivity among various rereferences revealed that IR could maintain a perfect performance similar to that of IR. The statistical contrast for schizophrenia in power and connectivity further indicated that REST could orient toward a recognizable characteristic for clinical research in diseases such as schizophrenia.

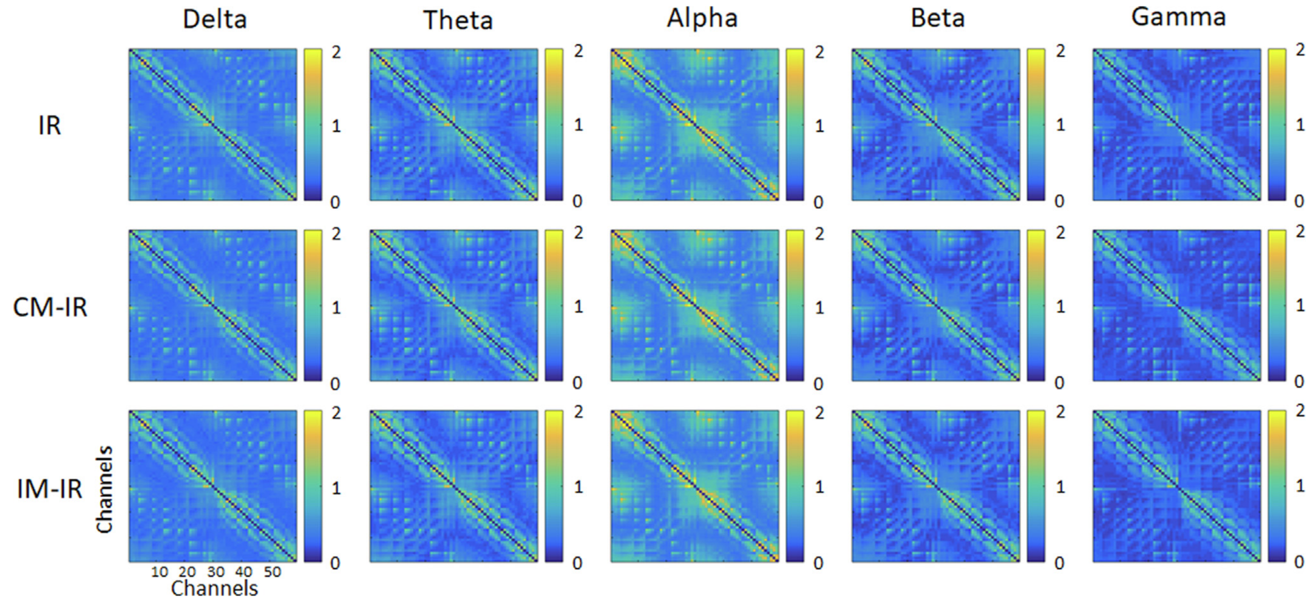

Fig. 5. Mean connectivities across subjects obtained from the IR signals (transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references). IR: infinity reference; IM: ipsilateral mastoid; CM: contralateral mastoid; REST: reference electrode standardization technique.

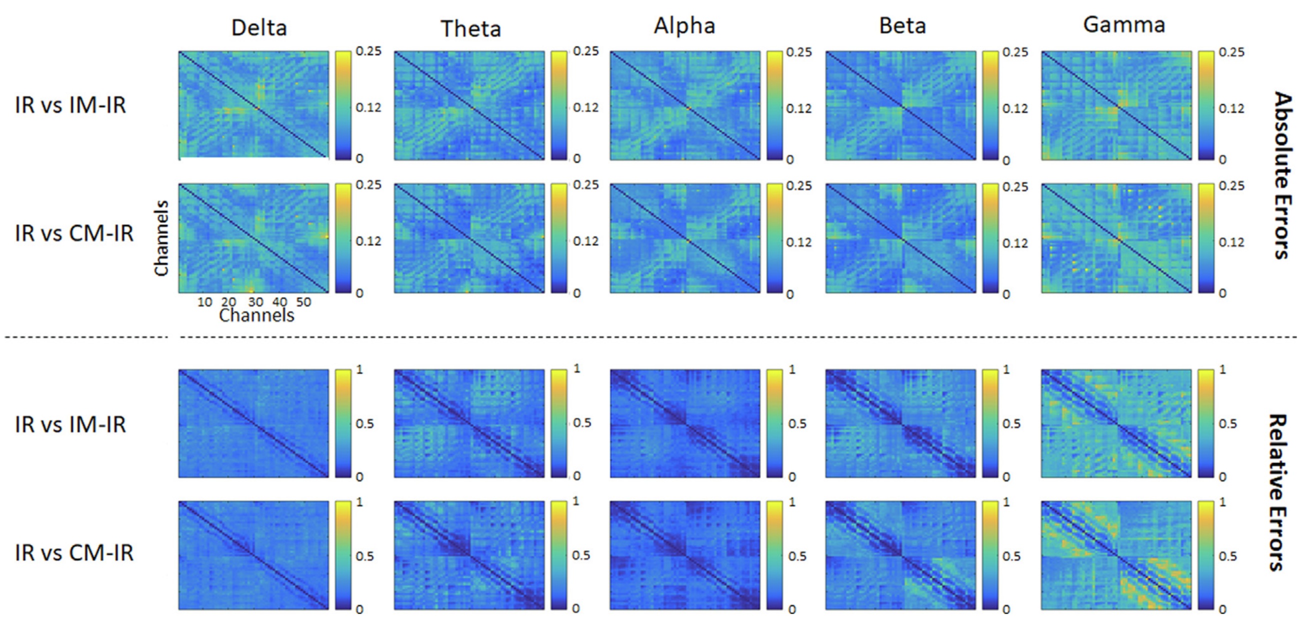

Fig. 6. Results of mean errors between connectivities obtained from the IR signals (transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references). IR: infinity reference; IM: ipsilateral mastoid; CM: contralateral mastoid; REST: reference electrode standardization technique.

4.1. Validation of REST transformation for nonunipolar mastoid reference

For unipolar montages, a desired offline rereferencing is commonly conducted by deducting the specified rereferencing signal from each channel to replace the original recording reference. This linear transformation could be written as a linear mathematical operation, and with this specific assumption, a vertex point of the scalp (Cz) (Lehmann et al., 1998), the average of the linked mastoids or ears (LM) (Gevins and Smith, 2000) and the average of all EEG channels (AR) (Offner, 1950) are all nonphysical, principle-based hypotheses (Yao, 2017). However, this conventional subtraction is invalid in many clinical cases when the monitoring of pathological EEG activities must be performed with a specific nonunipolar mastoid montage, such as the contralateral mastoids (CMs) or the ipsilateral mastoids (IMs) (Mercier et al., 2017, Michelmann et al., 2018). Because more than one independent recording reference is implied in the dataset, it cannot be solved simultaneously by any linear transform (Liu et al., 2015). To solve this problem, the reference electrode standardization technique (REST) was used to transform such nonunipolar mastoid montages and derive a computational zero reference at infinity (IR), and the performances of the REST method were investigated by calculating the absolute error, relative absolute error and Pearson's correlations (R) of signals/power/connectivity configurations between the IM/CM-IR references (IR transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references). As shown in Fig. 2A, and

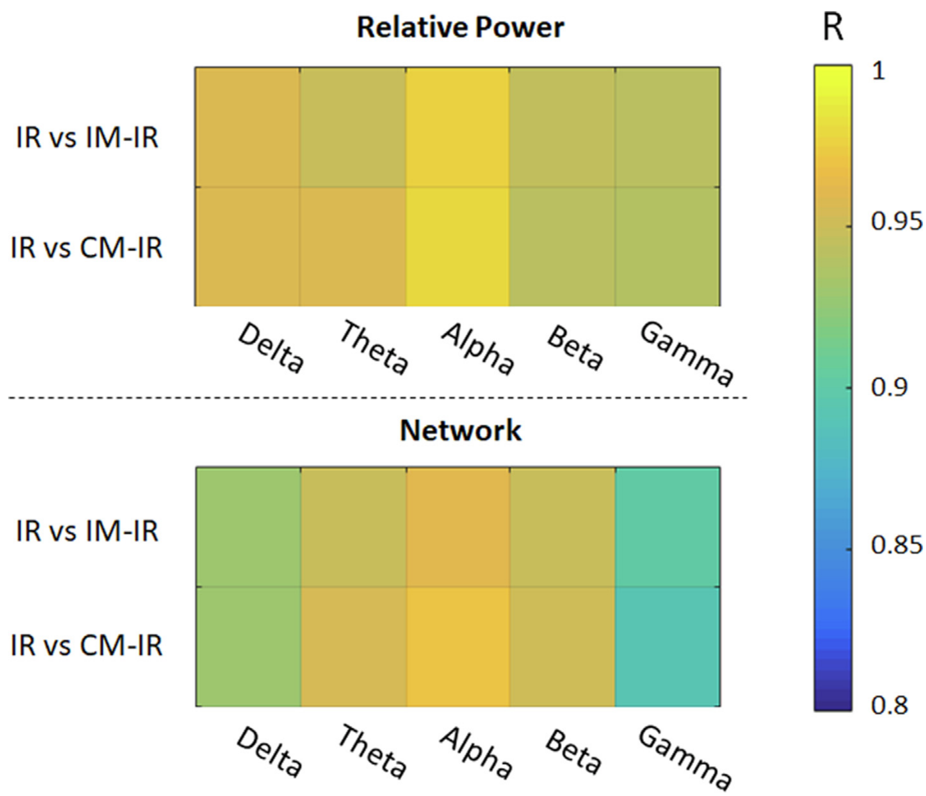

Fig. 7. Results of the mean spatial Pearson's correlations between power indices/connectivities obtained from the IR signals (transformed from nonunipolar mastoid references by REST) and the true IR signals (transformed from unipolar references). IR: infinity reference; IM: ipsilateral mastoid; CM: contralateral mastoid; REST: reference electrode standardization technique.

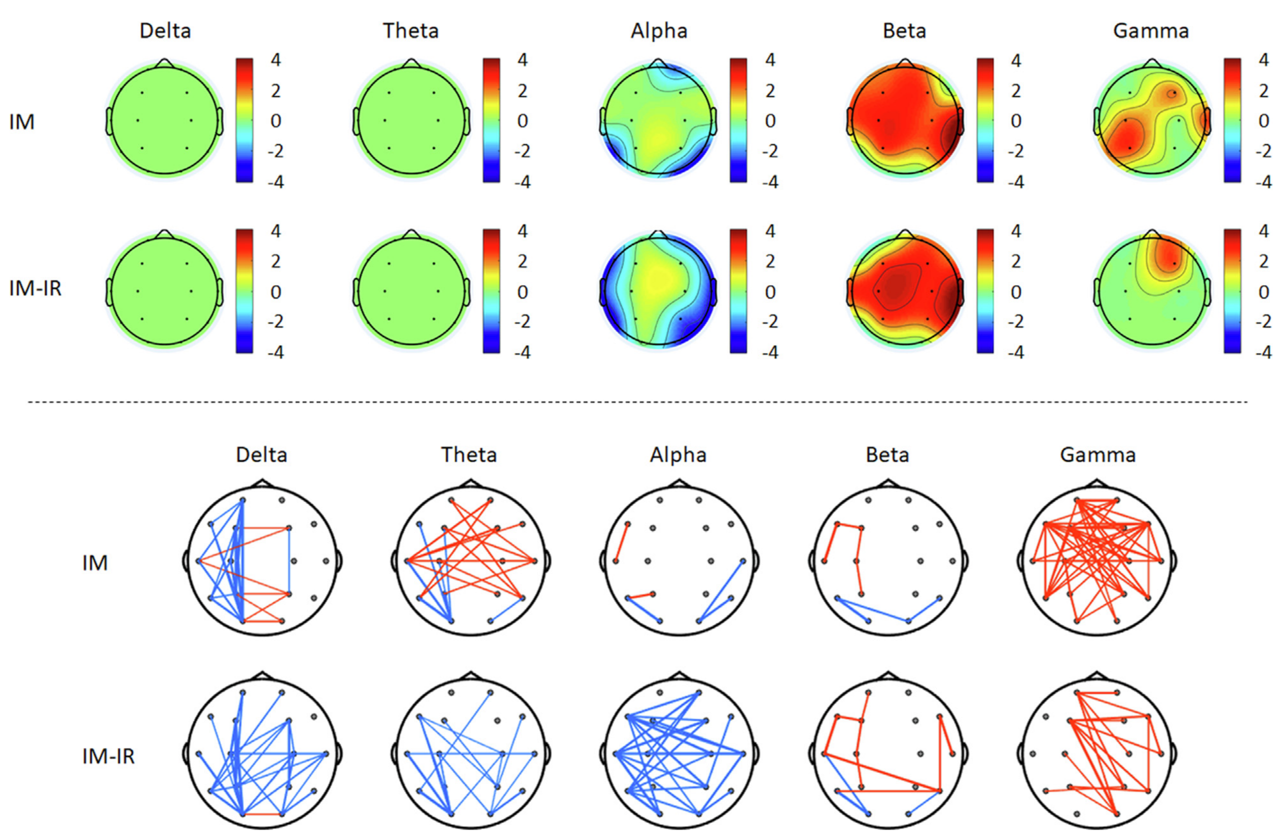

Fig. 8. Differences between power indices/connectivities of the schizophrenia and heathy control groups, with a reference of ipsilateral mastoids (IM) and a computational zero reference at infinity (IM-IR), respectively (up to bottom). The significance was set at P < 0.05. IR: infinity reference; IM: ipsilateral mastoid.

Figs. 3 and 5, the IM/CM-IR references were highly similar to the IR references in terms of the signals, spectral topography and connectivity configurations, respectively. REST also produced small errors and high correlations for both signals and power/connectivity configurations between the IM/CM-IR and true IR references (Figs. 2, 4, 6 and 7). REST, according to Eqs. (2) and (3), is based on the equivalent sources model (Geselowitz, 1998, Pascualmarqui and Lehmann, 1993), electrode montage and head model, and the transform matrix GG_{IM}^{+} that describes the relationship from the nonunipolar mastoid reference to the IR reference is physically based and reasonable (Dong et al., 2017, Hu et al., 2019, Yao, 2001, Yao et al., 2019). That is, REST has the ability to approximately convert a nonunipolar mastoid reference into a computational ideal zero reference and has physical meaning. In addition, considering that the IR reference can be easily transformed into any unipolar reference using a linear mathematical operation, for example, the performance of REST-produced AR was further investigated. As shown in Figures S1, S3 and S5, IM/CM-IR-AR references maintained high similarity with AR in terms of signals, spectral topography and connectivity configurations, respectively. In addition, REST produced small errors and high correlations (>0.9) for both signals and power/connectivity configurations between the IM/CM-IR-AR and true AR references (Figures S2, S4, S6 and S7). At the same time, previous studies have shown that the number of channels might affect the scalp EEG signals, and REST also produced higher errors of sparse channels (e.g., 16 channels) than that of high electrode density (Hu et al., 2018). As shown in Figures S8-S13, for signals and power/connectivity configurations (16 channels) between the IM/CM-IR and true IR references, REST produced higher errors and lower correlations (>0.64) than 59 channels, consistent with a previous study. These results implied that REST is a unique bridge linking the nonunipolar mastoid reference to the unipolar reference.

4.2. Feasibility of REST transformation in clinical EEGs

Next, the recording reference IM of the clinical EEGs was transformed by REST to derive a corresponding IR reference, and then the power and connectivity were estimated for each of those two references, i.e., IM and IM-IR. For the IM-IR reference, the spectral analyses revealed a frontoparietal alpha reduction, a general beta excess (located in the parietal, frontal and temporal areas) and a right frontal gamma excess. Simultaneously, the connectivity indicated a bilateral occipital-partial decrease in the delta and theta bands, a frontoparietal and occipital-partial decrease in the alpha band, a few partial increases in the beta band, and a right frontoparietal increase in the gamma band. Most studies in clinical schizophrenia have documented the presence of spectral abnormalities in schizophrenia populations and disconnections between large-scale functional brain networks (Di Lorenzo et al., 2015, Maran and Uhlhaas, 2016, Moran and Hong, 2011, Takahashi et al., 2018). Although the heterogeneity of schizophrenia, including pathophysiology, medication chronicity, illness progression and clinical symptoms, has a potential influence on related investigations, a broad consensus nonetheless has suggested deficient alpha power and increased beta and gamma activity (Boutros et al., 2008, Hughes and John, 1999, Moran and Hong, 2011). Correspondingly, the majority of studies that examined connectivity measures have reported connectivity anomalies in schizophrenia (Maran and Uhlhaas, 2016), with decreased delta connectivity in the fronto-partial (Tauscher et al., 1998) and temporal (Winterer et al., 2001) regions, decreased theta connectivity in the posterior temporal lobe areas (Tauscher et al., 1998, Winterer et al., 2001), and decreased alpha connectivity in the frontal (Hughes and John, 1999, Tauscher et al., 1998), fronto-posterior and parieto-temporal regions (Lehmann et al., 2014), which were more pronounced in the left hemisphere (Peng et al., 2013). Increased connectivity in the beta and gamma bands was reported, perhaps suggesting that connectivity was influenced by illness progression and clinical symptoms (Di Lorenzo et al., 2015). Consistent with these current studies, the statistical configurations of power and connectivity for schizophrenia implicated that the IR reference by REST could reveal the most recognizable characteristics of schizophrenia, while the original recording reference IM could induce some distinct deviations in the direction or location of contrast, especially in the connectivity estimation. In addition, it has also been confirmed in some simulations and real experiments that REST could significantly reduce the distortion of connectivity patterns compared to AR, Cz and LM references (Chella et al., 2016, Marzetti et al., 2007, Qin et al., 2010). It is thus suggested that REST could be applied in clinical EEGs with specific nonunipolar mastoid recording montages for offline analyses.

4.3. Virtues of REST and its perspective

Conventional offline subtraction rereference methods are invalid in clinical cases of a specific nonunipolar mastoid montage, such as the contralateral mastoids or the ipsilateral mastoids. Based on the physical principle-based hypotheses, REST can quickly and well rereference clinical EEGs with nonunipolar mastoid references to an approximate infinity reference. As a novel rereferencing method, REST has been integrated into the EEG preprocessing pipeline on the WeBrain cloud platform (https://webrain.uestc.edu.cn/) (Dong et al., 2021), as well as other EEG tool versions (https://www.neuro.uestc.edu.cn/name/shopwap/do/index/content/96) (Dong et al., 2017) and preprocessing pipelines and tools for simultaneous EEG-fMRI multimodal fusion (https://www.neuro.uestc.edu.cn/name/shopwap/do/index/content/101) (Dong et al., 2018). In addition, the online transforming version of REST may be need to further studied, which may facilitate online explorations of clinical EEG recordings.

4.4. Limitations

There are some of limitations in current studies. First, in the current work, it is not clear whether the differences found in schizophrenia patients reflect non-specific influences of attention, drug effects and perceptual sets etc. These influences may have some association with schizophrenia, but are not specific to cortical dysfunction. Therefore, it would be helpful to conduct applications with design controls such as ERP studies to further investigate the feasibility of REST in practical studies in the future. Second, the current work focuses on the offline REST transformation. For clinical EEGs, there may be potential influences of recording and movement artifacts on the REST display online, especially in displaying epileptogenic fields. Therefore, the online utilizations of REST may be need to further studied.

5. Conclusion

This study focused on whether the REST transformation could be adopted to resolve the offline rereferencing of clinical EEGs with a specific recording reference, which is resistant to traditional subtraction. Based on dataset 1 of laboratory EEGs, the comparison of signal, power and connectivity revealed that the computational IR signals transformed from nonunipolar mastoid references by REST could maintain high consistency with the true IR signals (transformed from unipolar references). The analysis of clinical schizophrenia EEGs with a recording reference of IMs indicated that the IR reference could orient toward a recognizable trait for the schizophrenia population. These analyses demonstrated that

REST might be an effective and robust resolution for these specific clinical EEGs and could therefore retrieve these data for further analysis by deriving a favorable offline reference IR.

Author contributions

Conceived and designed the work: Dezhong Yao; Data Acquiring: Mingjun Duan, Xiyu Cai, Yun Qin, Pan Huang and Cheng Luo; Data Analyzing: Yongxiu Lai, Li Dong, Liping Wang, Yongtao Wang and Huizhen Cui; Paper writing: Li Dong and Yongxiu Lai. All authors revised the work for important intellectual content. All the authors have read and approved the manuscript.

Data and Code Availability Statements

The datasets and codes used in this study are available on reasonable request to the corresponding author.

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.03.361.

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