An EEG-based marker of functional connectivity: detection of major depressive disorder

Ling Li • Xianshuo Wang • Jiahui Li • Yanping Zhao
Presentation's author: Bianca-Georgiana Talaba

THE ARTICLE

Cognitive Neurodynamics (2024) 18:1671–1687
https://doi.org/10.1007/s11571-023-10041-5

RESEARCH ARTICLE

An EEG-based marker of functional connectivity: detection of major depressive disorder

Ling Li[1] · Xianshuo Wang[1] · Jiahui Li[1] · Yanping Zhao[1]

Received: 28 April 2023 / Revised: 15 September 2023 / Accepted: 9 November 2023 / Published online: 1 December 2023

- «Cognitive Neurodynamics» is an international, interdisciplinary, peer-reviewed journal, focused on Neuroscience, Mathematics, Physics, Computer Science, Robotics and many more;
- Volume 18, pages 1671–1687, (2024);
- Research article.

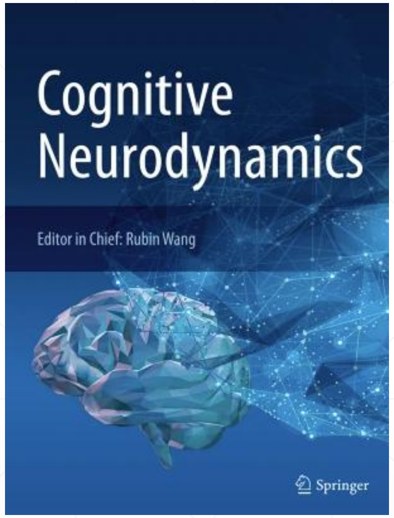

Fig. 1 Cognitive Neurodynamics.

MAJOR DEPRESSIVE DISORDER (MDD): Definition

According to the Diagnostic And Statistical Manual Of Mental Disorders 5-TR (DSM-5-TR, 2023), Major depressive disorder (MDD) is a psychiatric disorder characterized by at least 5 of the following symptoms during the same two week period:

- depressed mood;
- loss of interest/pleasure;
- weight loss or gain loss;
- insomnia or hypersomnia;
- psychomotor agitation or retardation;
- fatigue;
- feeling worthless or excessive/innapropriate guilt;
- decreased concentration;
- thoughts of death/suicide.

MAJOR DEPRESSIVE DISORDER (MDD): Implications

Major Depressive Disorder can cause:

- severe functional impairment;
- interpersonal relationship issues;
- a low quality of life;
- anxiety disorders;
- the risk of suicide.

It can also aggravate medical ilnesses such as diabetes and hypertension (Navneet Bains & Sara Abdijadid, 2023).

MAJOR DEPRESSIVE DISORDER (MDD): Diagnosis

MDD is diagnosed by a mental health professional, based on a combination of clinical assessment, interviews, and standardized diagnostic criteria, such as:

- Patient Health Questionnaire-9 (PHQ-9);
- Hamilton Rating Scale for Depression (HAM-D);
- Montgomery-Asberg Depression Rating Scale (MADRS);
- Beck Depression Inventory (BDI) (Navneet Bains & Sara Abdijadid).

→ **Functional brain connectivity** and **Deep Learning** can also provide help for the detection of MDD as an additional diagnostic tool.

ELECTROENCEPHALOGRAPHY (EEG)

The datasets used in this study were collected using Electroencephalogram (EEG).

EEG has got the following characteristics:

- minimal cost;
- it is painless;
- non-invasive acquisition;
- high temporal resolution.

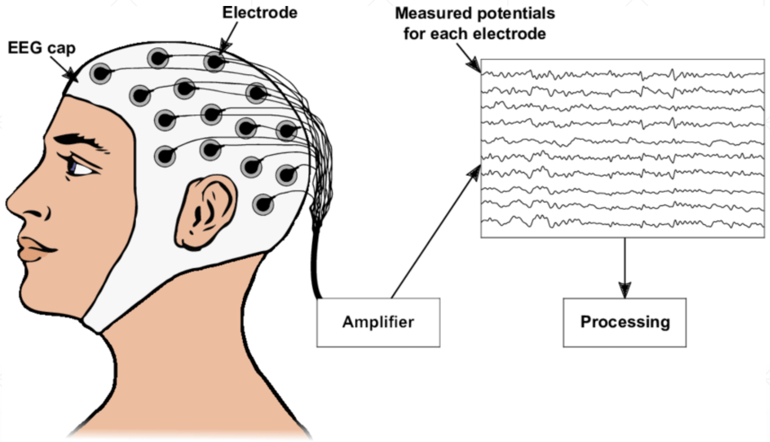

Fig. 2 Sebastian Nagel (2019).

It has got many channels to record brain activity. The electrodes are positioned on the scalp using a cap. The recorded signal represents the electrical activity of the brain's pyramidal neurons. The output is composed of signals measured in microvolts (µV).

EEG can be useful in many psychiatric disorders, such as MDD, by mapping brain connectivity (Allen et al. 2014; Babiloni et al. 2005; Drysdale et al. 2017; Fu et al. 2021; Sakkalis 2011; Whitfield-Gabrieli et al. 2012).

THE AIM OF THIS STUDY

Previous work
(Li et al., 2020; Mohammadi et al., 2021)

- Focus on **phase synchronization** to assess brain connectivity;
- primarily consider the phase differences between EEG signals without accounting for amplitude variations;
- overlook the impact of signal strength and instantaneous frequency variations.

The present research

- Combines both **phase synchronization** and **amplitude coherence** using synchrosqueezed wavelet coherence (SWC);
- it introduces a new marker, P-MSWC, to evaluate connectivity in time, frequency, and phase domains;
- employs a lightweight CNN for effective MDD detection with superior results on public datasets.

MATERIALS AND METHODS

Participants, datasets and pre-processing;

Feature extraction;

- *Synchrosqueezed wavelet transform (SWT);*
- *Coherence function and synchrosqueezed wavelet coherence;*
- *Phase locking value;*
- *Feature fusion and functional connectivity matrix.*

Classification:

- *Deep neural network;*
- *Statistical analysis;*
- *Validation methods.*

Participants and datasets

Dataset 1 (Mumtaz et al. (2017))

- **Experimental group**: 28 MDD patients (Age, Mean=40.33, SD=± 12.861);
- **Control group**: 27 healthy subjects (Age, Mean = 38.227, SD = ± 15.640).

Data used: Resting eyes-closed EEG.

Patients were diagnosed according to the DSM-IV criteria at the University of Sains Malaysia (HUSM).

Dataset 2 (James F. Cavanagh et al. (2019))

- **Experimental group** (DEP): 22 MDD patients with BDI score > 13;
- **Control group** (CTL): 22 participants with BDI score <7.

Data used: Resting-state EEG.

Table 1 Details of the participants.

Characteristic	CTL	DEP
Male[nos.]	8	8
Female[nos.]	14	14
Age[years]	19.00(± 1.14)	18.91(± 1.31)
BDI score	0.50(± 0.66)	21.82(± 5.56)
TAI score	28.95(± 4.20)	56.15(± 6.94)

Pre-processing

Dataset 1

- 5 minute resting state EEG with eyes closed;
- 19 channels using 10-20 electrode placement system;
- BrainMaster Discovery 24E amplifier;
- Linked ears used as reference.

Dataset 2

- 64 channel EEG using SynAmps2 system;
- Bandpass filter (0.5-100 Hz), 500 Hz sampling rate;
- 1 offline reference mean mastoid;
- only 19 channels out of 64 were retained (corresponding to Dataset 1).

Pre-processing

- Sampling frequency standardized to **256 Hz** for both datasets;
- Notch filter applied to suppress **50 Hz** noise;
- Bandpass filter: **0.5 – 70 Hz**;
- **Artifact removal** (EEG toolbox used, artifact subspace reconstruction (ASR));
- **Data augmentation**.

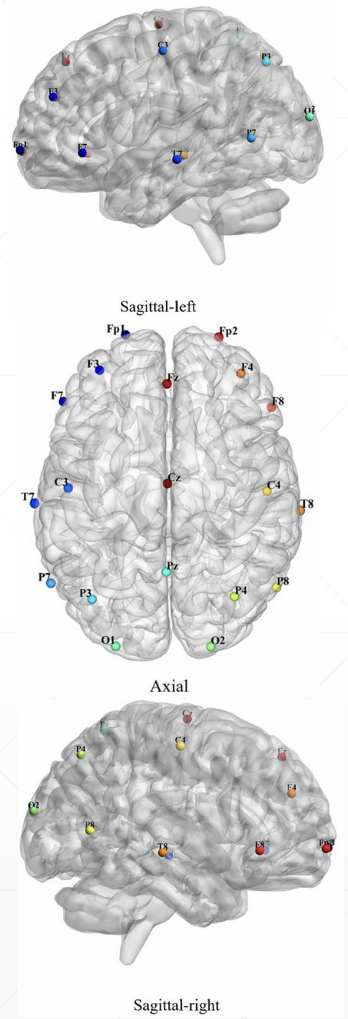

Fig. 3 Spatial locations of the 19 electrodes.

Feature extraction
Synchrosqueezed wavelet transform (SWT)

Continuous Wavelet Transform (CWT)

- Ideal for time-frequency analysis of non-stationary signals, like EEG or other biological signals (frequency changes over time);
- Represents signals as 2D functions of time and frequency.

Discrete Wavelet Transform (DWT)

- Non-redundant, highly efficient wavelet representation;
- Orthogonal basis of wavelets (finite number of coefficients) → computational efficiency.

Synchrosqeezed Wavelet Transform (SWT)

- Combines CWT with time-frequency rearrangement;
- Inspired by empirical mode decomposition (EMD);
- Effective at reducing noise interference;
- Provides clearer time-frequency representations, suitable for noisy physiological signals.

Mathematical approach to calculate the SWT (with MATLAB R2021a)

1. Selection of a **suitable wavelet basis function** (wavelet family).
2. Application of **CWT** to the signal s(t) to obtain the **wavelet coefficients W_s(a,b)**

$$W_s(a,b) = \int s(t) \frac{1}{\sqrt{a}} \overline{\psi(\frac{t-b}{a})} dt$$

where s(t) is the time domain signal, a is the scale factor, b is the time shift factor, $\overline{\psi(t)}$ is the conjugate of the wavelet basis function;
3. Trasformation of the **CWT** of the signal **into the frequency domain** (Plancherel's theorem) using the Fourier Transform;
4. Calculation of **the instantaneous frequency of the signal** (wavelet coefficients from time-scale domain to time-frequency domain);
5. Calculation of **SWT(ω,b)** and conversion to the frequency-time domain ($f = \omega/2\pi$).

Wavelet coherence (WC) vs. Synchrosqueezed wavelet coherence (SWC)

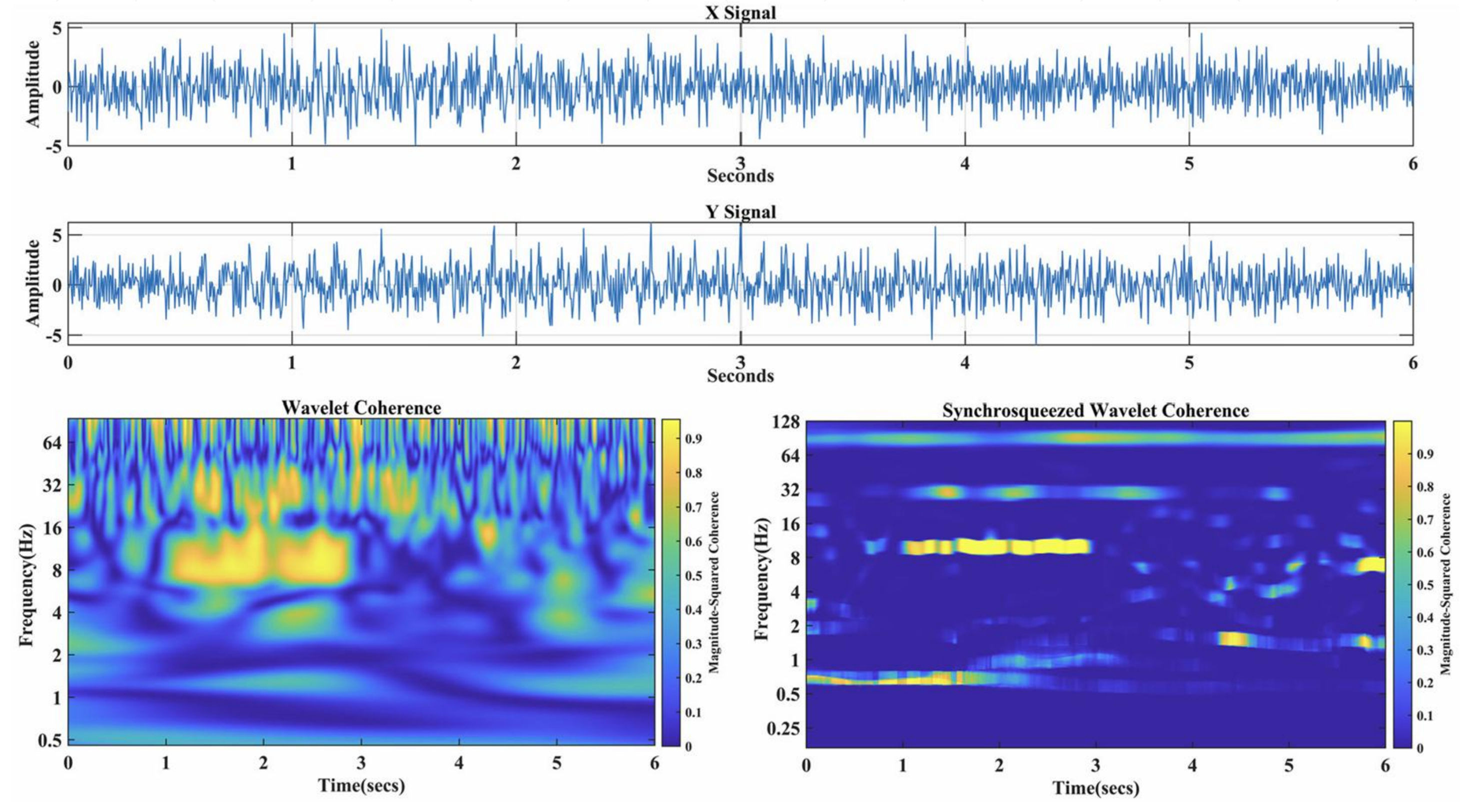

Fig. 4 WC vs. SWC.

WC: examines the correlation in time-frequency domain between two time series by calculating power spectral density.

SWC: uses SWT instead of CWT.

In figure 4: WC cannot detect the relationship between the two simulated noisy signals (x(t) and y(t)) well at 90 Hz and has poor accuracy at 30 Hz. SWC is more accurate in detecting relationships and more resistant to noise.

Phase locking value (PLV)

PLV is an important method for the investigation of brain functional connectivity, by isolating phase information from the signal and then calculating the **absolute value of the average phase difference** between the two signals.

$$PLV(f) = \left|\left\langle e^{i\phi_{x,y}(f,t)} \right\rangle\right| = \left| \frac{1}{N} \sum_{n=1}^{N} e^{i\phi_{x,y}(f,t_n)} \right|$$

Where $|\langle * \rangle|$ indicates the time average, N is the number of sampling points.

$$0 \leq PLV(f) \leq 1.$$

PLV→1 (strong phase synchronization between two signals);

PLV→0 (weak phase syncronization).

Feature fusion and functional connectivity matrix

MSWC: average of the SWC value in the time dimension to represent the average coherence degree of the two signals in the frequency dimension.

PLV + MSWC → P-MSWC

According to the formula: $P - MSWC(f) = F\left(PLV(f) + MSWC(f)\right)$,

where F(*) is a mapping function.

P-MSWC is used to construct a novel connectivity matrix of the EEG signals, which will be the input of the Convolutional Neural Network.

Classification
Deep neural network

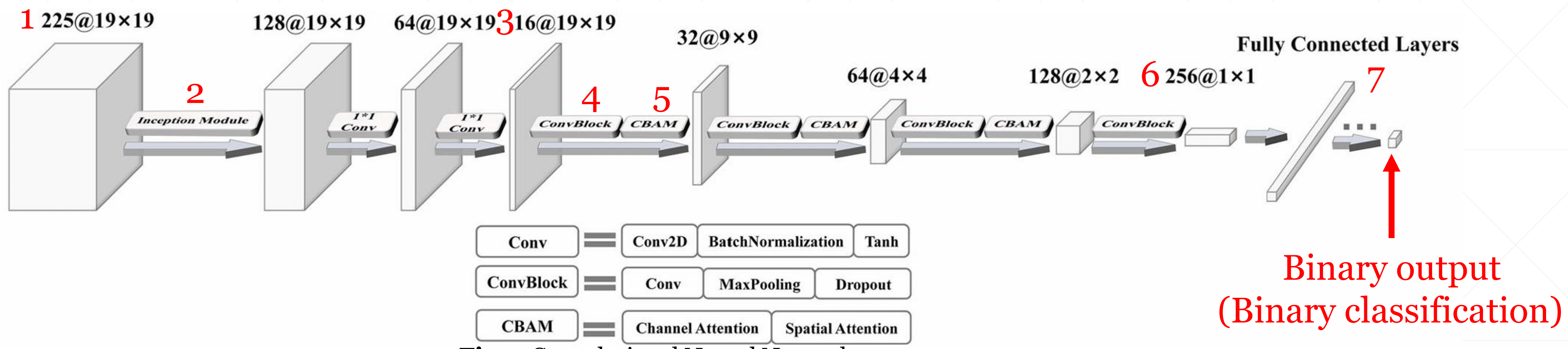

Fig. 5 Convolutional Neural Network.

1 **Input matrix** (**225x19x19**: 19-channel connectivity matrix + 225 frequency dimension): EEG data in 3D matrix;
2 Inception module: Utilizes convolutional filters of various sizes (1x1, 3x3, 5x5) to capture features at different spatial and temporal scales;
3 **Dimensionality reduction** from 225x19x19 to **64x19x19** using 1*1 convolutions;
4 ConvBlock: 2D convolutions + maxpooling + dropout;
5 CBAM: Channel attention + Spatial Attention;
6 Dimensionality reduction from 64x4x4 to **256x1x1**;
7 Fully connected layers + sigmoid activation function applied on the output layer: probability value that indicates if the participant belongs to the MDD group or healthy group.

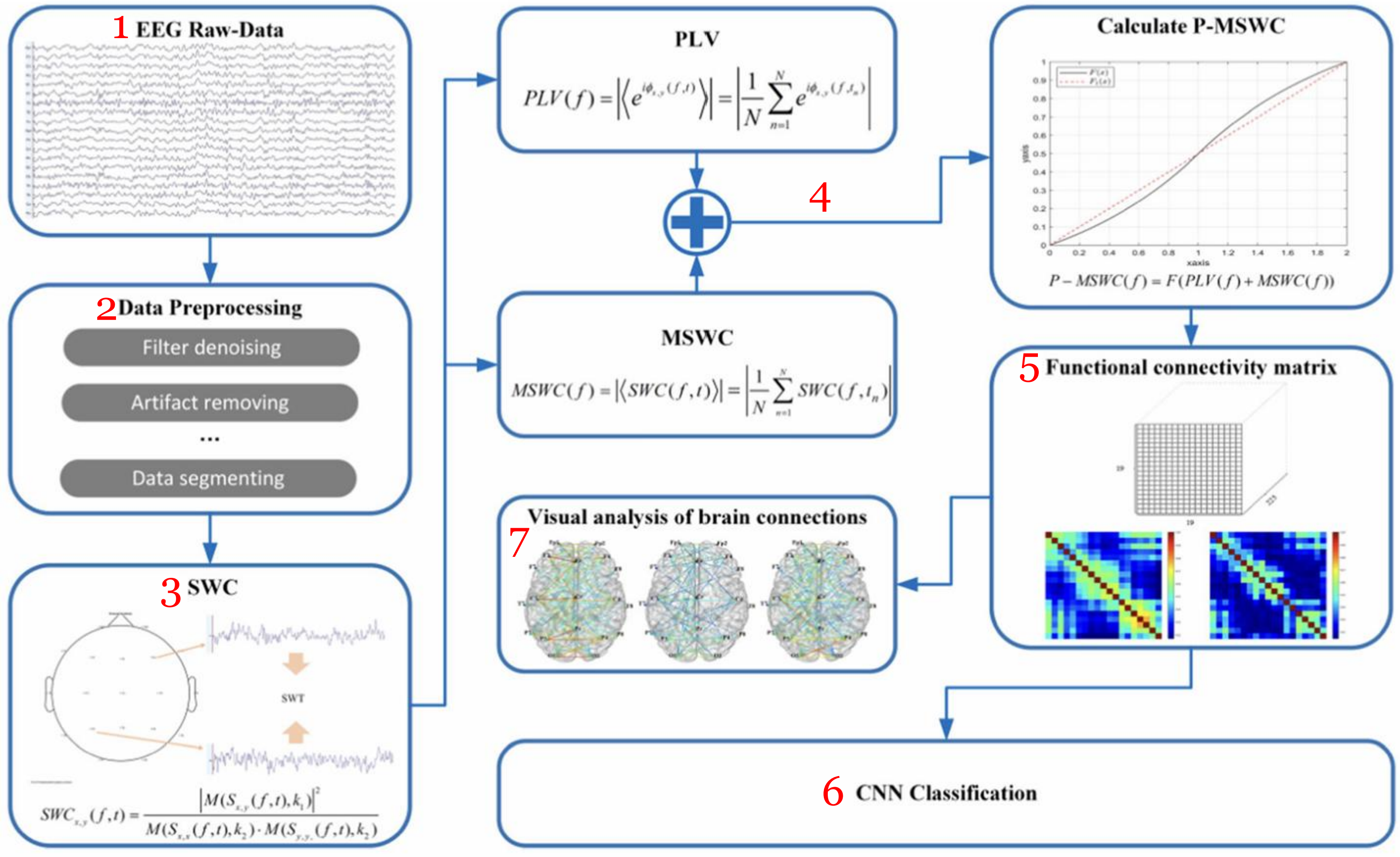

Fig. 6 Process for the MDD detection described in this paper.

1-2 The raw EEG signals are pre-processed. The process is described in detail in the "Dataset and pre-processing" section.

3-4 The feature P-MSWC is extracted by fusing MSWC and PLV features. The details are described in the "Feature extraction" section.

5 The fused feature is utilized to construct the brain functional connectivity matrix.

6 The CNN network is used to detect MDD. The process is described in detail in the "Classification" section.

7 The connection matrix is visualized and analyzed. The details are in "Results" section.

Statistical analysis

The Mann–Whitney U test is a non-parametric hypothesis test, in which the **null hypothesis** is **rejected** when the **p-value** is **less than 0.05**, and the difference is **statistically significant**.

The article uses the Mann–Whitney U test to verify whether the **fusion features** of the **MDD patients** and **control group** are **significantly different** to demonstrate the validity of the features.

Validation methods

Metrics evaluated:

$$Sensitivity(\%) = \frac{TP}{TP + FN} \times 100$$

$$Specificity(\%) = \frac{TN}{TN + FP} \times 100$$

$$Accuracy(\%) = \frac{TP + TN}{TP + TN + FP + FN} \times 100$$

where TP, TN, FP and FN are true positive, true negative, false positive and false negative respectively.

RESULTS

2 datasets: 49 healthy controls + 50 MDD patients.

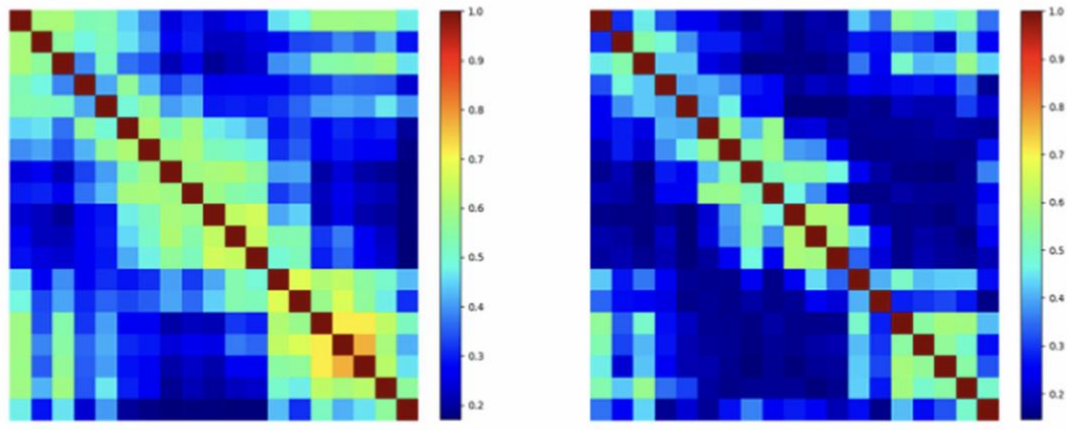

Fig. 7 19x19 2D connectivity diagram.

Left: average functional connectivity matrix for a **healthy** participant in **gamma band**.

Right: **MDD** participant in gamma band.

A larger value of the connectivity matrix (red color) represents a greater correlation between two channel pairs.
The results of this study are based on five EEG frequency bands, which are delta (0.5—4.0 Hz), theta (4.0—8.0 Hz), alpha (8.0—13.0 Hz), beta (13.0—30.0 Hz) and gamma (30.0—70.0 Hz).

Results of Mann–Whitney U test

Table 2 P-values for different frequency bands for each dataset.

Frequency bands	Dataset 1	Dataset 2	Combined dataset
Delta	5.2193e-01	2.2504e-05	1.4911e-07
Theta	6.1758e-36	6.8333e-06	3.0118e-82
Alpha	7.4581e-23	1.7091e-02	2.2544e-24
Beta	1.1515e-11	5.0374e-09	2.0723e-33
Gamma	8.0923e-36	1.0922e-04	8.7634e-58
Full-band	4.6016e-89	1.3005e-13	7.4934e-99

Smaller p values = larger differences in groups (healthy and MDD).

Results of hold-out method

70% training set (6729 samples) + 30% test set (2885 samples);

100 epochs, mini batch size=32, Adam Optimizer, learning rate=0.0001;

Loss functions=binary cross-entropy.

Table 3 Best accuracy, sensitivity, and specificity of Dataset 1, Dataset 2, and Combined dataset using 100 epochs of training.

Dataset no.	Accuracy (%)	Sensitivity (%)	Specificity (%)
Dataset 1	99.87	100.00	99.75
Dataset 2	93.93	94.44	93.45
Combined dataset	97.16	97.08	97.24

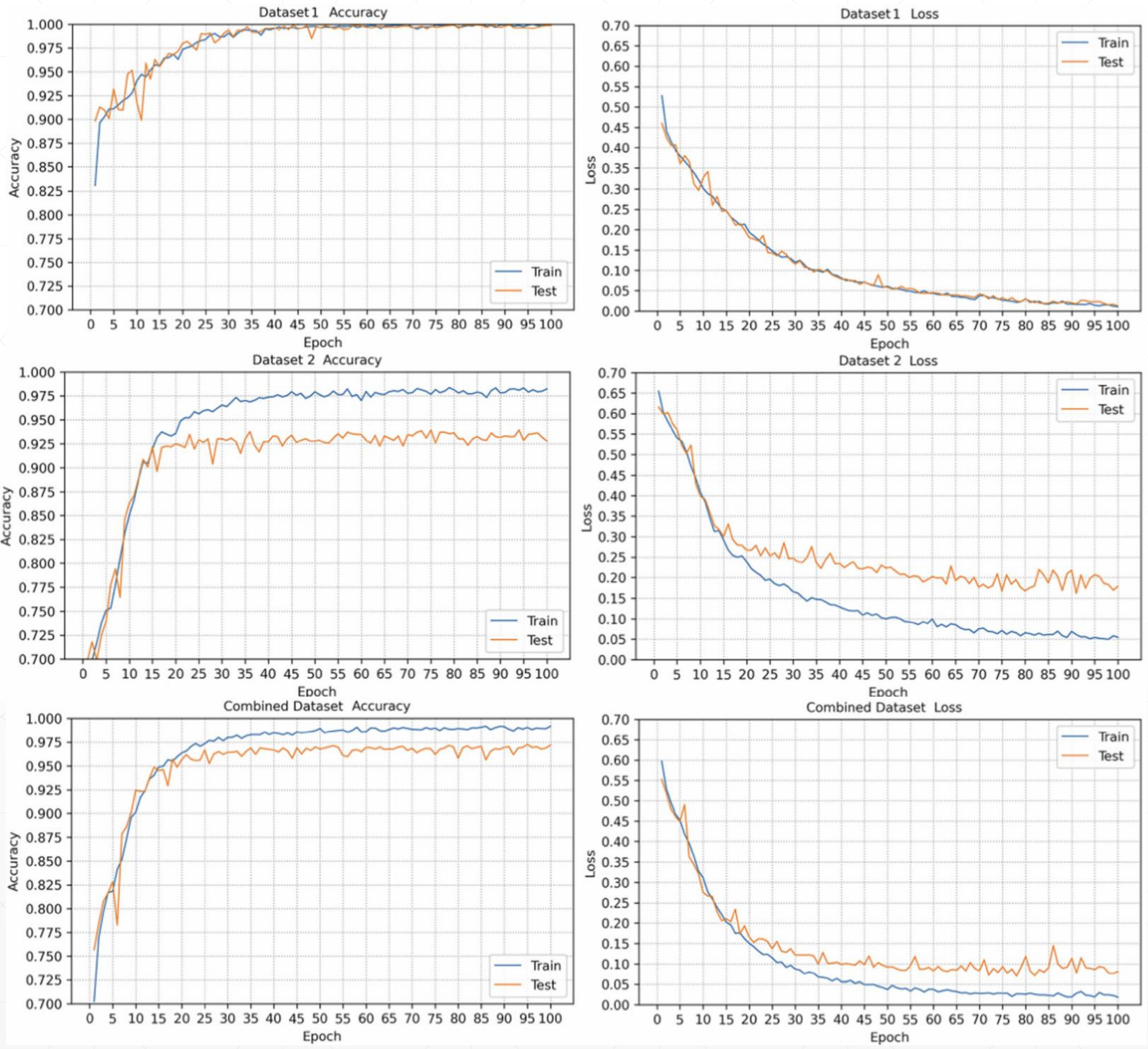

Fig. 8 Accuracy and loss curves for Dataset 1, Dataset 2 and Combined dataset.

Comparison with other machine learning classifiers

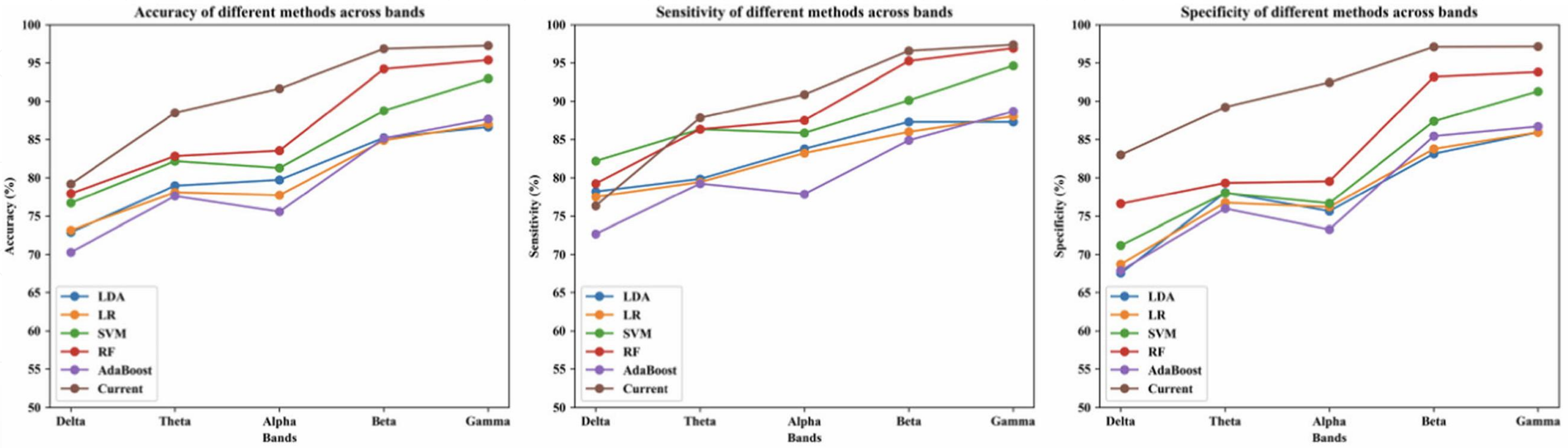

Fig. 9 The results of different methods in various frequency bands.

The results indicate that the performance of all algorithms improves as the frequency band increases, with the beta and gamma bands showing the best results. This suggests that higher frequency bands may contain more critical information for differentiating MDD than lower frequency bands.

MDD patients:

δ: Increase in total connection strenghts;

θ: reduction in connections in the temporal and central regions;

α: reduction of the number of connections+increase in the total strength of connections in frontal regions;

β: unchanged number of connections + slight increase in strength in central regions;

γ: significant reduction in the number and strength of connections, particularly between central and parietal regions, along with decreased connection strength in the occipital lobe (T7, O1, F8, C3 channels).

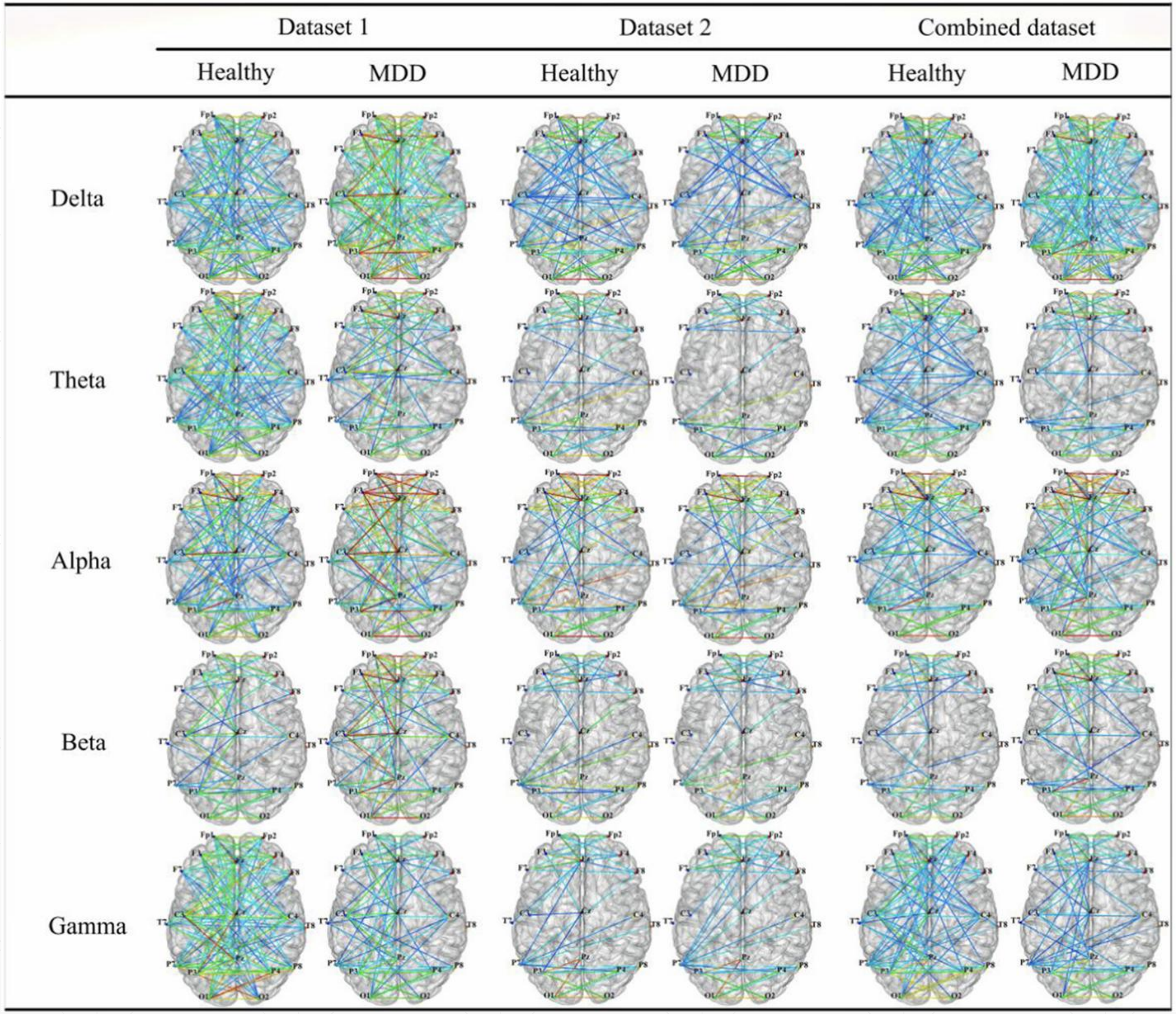

Fig. 10 Sample connectivity of different datasets. Red lines: bigger brain connection values; blue lines: smaller values.

DISCUSSION AND CONCLUSION

Strengths

- Use of P-MSWC which improves noise resistance and time-frequency localization in EEG signal analysis;
- use of a CNN with improved classification performance.

Limitations

- Small sample size;
- lack of large-scale open-source datasets;
- missing values.

Findings

- Significant reduction in gamma band connectivity in MDD patients, particularly between left and right hemispheres.

Future Directions

- Extension of the application of this method to other neurological disorders like ADHD;
- creation of larger, standardized datasets for improved diagnosis and treatment of MDD.

References

- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596
- Bains N, Abdijadid S. Major Depressive Disorder. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559078/
- Li, L., Wang, X., Li, J. et al. An EEG-based marker of functional connectivity: detection of major depressive disorder. Cogn Neurodyn 18, 1671–1687 (2024). https://doi.org/10.1007/s11571-023-10041-5
- Nagel, Sebastian. (2019). Towards a home-use BCI: fast asynchronous control and robust non-control state detection. 10.15496/publikation-37739

Thank you for your attention!

Any questions?