Intersubject Variability in Classification Models for Brain-Computer Interfaces

Eduardo V. Pérez-Hernández, Margarita Aviña-Corral, Zaida Adriana Gárate-Cahuantzi, J. A. Carrasco-Ochoa, José Fco. Martínez-Trinidad, Alejandro A. Torres-García

Instituto Nacional de Astrofísica, Óptica y Electrónica, Computer Sciences Department, Sta. María Tonantzintla, Puebla, México {eduardo.perezherna,margarita.avina,zaicahuantzi,ariel,fmartine,alejandro.torres}@inaoep.mx

Abstract. Intersubject variability in electroencephalography (EEG) signals presents a significant challenge in developing motor imagery-based brain-computer interface (BCI) systems. This study investigates the impact of different training strategies using Dataset IVa from the BCI Competition III, which involves classifying imagined motor tasks in healthy individuals. Building upon recent successful methodologies, we employ a feature extraction pipeline based on Common Spatial Patterns (CSP) across multiple frequency sub-bands, followed by classification using Linear Discriminant Analysis (LDA) and Support Vector Machines (SVM). We evaluate four training schemes: (1) subject-specific models, (2) a multisubject model trained on all subjects, (3) models trained exclusively on high-performing subjects, and (4) models trained only on lowperforming subjects. The subject-specific model achieved the highest accuracy (90.71%), while the multisubject model yielded a competitive performance of 88.14%, without requiring individual calibration. Training on high-performing subjects achieved moderate generalization (75.71%), whereas using low-performing subjects resulted in a marked drop in accuracy (65.57%). These findings highlight the importance of subject diversity in training datasets and suggest that generalized models can approach the performance of subject-specific models while enhancing usability in real-world, calibration-free BCI applications.

Keywords: Intersubject Associativity, EEG, BCI, Motor Imagery.

1 Introduction

EEG-based brain-computer interfaces have shown great potential in clinical applications, particularly for motor rehabilitation and the control of assistive devices. One of the most studied paradigms in this context is motor imagery (MI), where users imagine a movement without physically performing it. This process generates distinctive patterns in sensorimotor rhythms (SMRs), which can be detected and analyzed for classification tasks [8].

Despite advances in signal processing and machine learning, EEG signals exhibit substantial variability that impairs the reliability and scalability of BCIs. This variability manifests in two primary forms: intersubject and intrasubject variation. Intersubject variability arises from intrinsic differences between individuals, such as age, skull thickness, brain anatomy, or signal-to-noise ratios [2]. In contrast, intrasubject variability reflects fluctuations within the same person, caused by factors such as fatigue, attention level, mood, or electrode placement [12]. Both types of variability alter the statistical properties of EEG features and significantly hinder the generalization ability of machine learning models [9].

This variability represents one of the significant challenges for implementing BCIs, limiting their effectiveness and performance in practical applications. One of the consequences of this challenge is the phenomenon known as BCI illiteracy, where a subset of users is unable to achieve satisfactory control of the system. To address these challenges, several research efforts have focused on understanding the causes of BCI illiteracy [11, 3] and on improving classification performance through machine learning (ML) techniques [14, 5, 13].

In this study, we explore both types of variability in the context of motor imagery classification. Our goal is to assess the impact of intersubject and intrasubject variation and to evaluate whether incorporating data from multiple subjects can improve generalization—especially for low-performing users—without requiring subject-specific calibration. Specifically, we analyze the relative impact of each type of variation on the classification accuracy of MI EEG signals, using the BCI Competition III Dataset IVa [4]. To do so, we design a series of experiments that evaluate a classification strategy based on data from multiple subjects, intended to enhance generalization—particularly for individuals who typically perform poorly in MI-based tasks. Specifically, we conducted: (1) training on a single subject and evaluating on all others, (2) training exclusively on high-performing subjects, (3) training on low-performing subjects, and (4) training on all subjects—referred to as the multisubject approach.

The remainder of this paper is structured as follows. First, Section 2 presents related work, focusing on the most widely used methods and recent contributions addressing subject variability. Section 3 describes the proposed approach followed in this paper, including the procedures for feature extraction and the evaluation protocols designed to assess intra- and intersubject performance. Section 4 details the dataset used in our study, including trial structure, subject information, and the process by which trials were labeled. In Section 5, we report our experimental results. Finally, in Section 6, we expose our conclusions and some directions for future work.

2 Related Work

The success of motor imagery-based brain-computer interface (MI-BCI) systems relies heavily on effective signal processing and robust feature extraction. EEG signals are inherently noisy, possess a low signal-to-noise ratio, and exhibit sig-

nificant inter- and intrasubject variability, making it critical to apply techniques that can isolate meaningful patterns related to imagined movements.

Among the most widely adopted methods for spatial feature extraction in MI-BCI is the Common Spatial Pattern (CSP) algorithm. CSP works by deriving spatial filters that maximize the variance of one class while minimizing it in the other [16]. This projection enhances class-separable patterns by reducing the multichannel EEG data into a more discriminative subspace. Its effectiveness, however, is sensitive to the selected time windows and frequency bands.

To overcome these limitations and improve generalizability, several CSP variants have been proposed. A prominent example is the Filter Bank Common Spatial Pattern (FBCSP) method [1], which decomposes EEG signals into multiple frequency subbands using a filter bank. CSP features are then extracted independently from each subband, allowing the model to capture subject-specific frequency dynamics. This approach has shown improved robustness in scenarios where motor imagery characteristics vary substantially between individuals.

Classification plays a central role in translating these extracted features into actionable BCI commands. Traditional machine learning techniques such as Linear Discriminant Analysis (LDA) and Support Vector Machines (SVM) remain popular choices in MI-BCI research due to their simplicity, interpretability, and good performance with low-dimensional features. These methods have frequently been applied on CSP or FBCSP-based feature sets and are particularly well-suited for small to medium-sized datasets.

Table 1 summarizes representative results from the literature on the BCI Competition III Dataset IVa under intrasubject evaluation settings. For example, Shiam et al.[10] achieved a mean accuracy of 91.36% using FBCSP and SVM, while Kabir et al.[6] reported 91.43% by applying the ReliefF feature selection with LDA. Other approaches, such as evolutionary optimization (e.g., WCSP + BPSO)[7] and deep learning with target subject re-tuning (TSRT)[15], have also demonstrated competitive performance.

Table 1. Performance comparison in terms of MI classification accuracy on BCI Competition III Dataset IVa.

Study	Method	aa	al	av	aw	ay	Mean
Shiam et al.[10]	FBCSP + SVM	86.43	97.86	78.93	97.86	97.86	91.36
Kabir et al.[6]	ReliefF + LDA	89.29	98.57	75.36	97.51	96.43	91.43
Petrov et al.[7]	WCSP + BPSO	90.10	83.60	92.00	90.90	94.10	90.30
Zaremba et al.[15] TSRT + CNN	81.00	94.10	64.10	92.10	93.60	85.00

While more recent developments in deep learning and transfer learning have shown promise—especially in subject-independent contexts—their applicability is often limited by the need for large annotated datasets and high computational resources. In contrast, CSP combined with classical classifiers like LDA and SVM continues to offer a favorable balance between performance and efficiency in practical BCI systems.

3 Proposed Approach

This section details the proposed approach followed in our study, detailing the feature extraction pipeline, the multi-subject evaluation framework, and the classification strategy designed to assess inter- and intrasubject variability in motor imagery EEG signals.

Feature Extraction Pipeline. To generate individual subject feature vectors, the preprocessed EEG signals were decomposed into four frequency sub-bands commonly associated with event-related desynchronization (ERD) and event-related synchronization (ERS): mu (8–13,Hz), low beta (13–22,Hz), high beta (22–30,Hz), and the full band (8–30,Hz). For each sub-band, Common Spatial Pattern (CSP) analysis was independently applied to extract three features that maximize the discriminability between the two motor imagery classes (left vs. right hand). This resulted in a 12-dimensional feature vector per trial (3 features \times 4 bands). This procedure was applied individually for each subject. The full filter bank and CSP-based feature extraction pipeline is illustrated in Fig. 1.

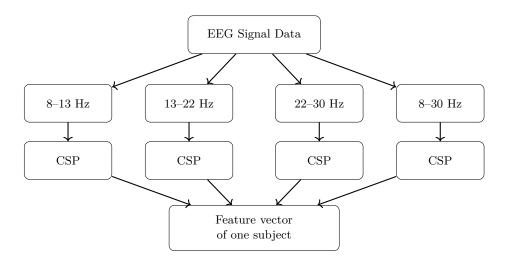


Fig. 1. Filter bank decomposition and CSP-based feature extraction for individual subjects.

Multi-Subject Training Framework. To evaluate the generalization capability across subjects, we implemented a multi-subject training framework illustrated in Fig. 2. Feature vectors were computed independently for each subject and then concatenated according to different training strategies. Before classification, the feature matrix was normalized using min-max scaling, applied globally across all features to ensure consistency between subjects and reduce intersubject amplitude differences. Four training strategies were designed:

- Training on a single subject and evaluating on all other subjects, allowing us to assess the model's ability to generalize from individual data to unseen users
- Training exclusively on high-performing subjects to determine whether their neural patterns could improve classification performance in other users.
- Training solely on low-performing subjects to evaluate the impact of limited representations.
- Training on all available subjects, referred to as the multisubject approach, which aims to create a more generalized representation by leveraging intersubject variability.

This framework allows for a systematic comparison of training conditions and highlights how subject-specific information influences cross-subject decoding performance.

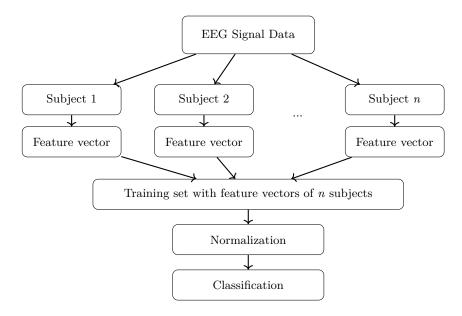


Fig. 2. Framework for multi-subject feature vector extraction and classification.

Evaluation Protocol. Model performance was assessed using stratified 5-fold cross-validation to ensure a balanced evaluation. For each fold, 80% of the available trials were used for training and the remaining 20% for testing. Stratification was performed independently for each subject to preserve the class distribution across folds, ensuring a proportional representation of left- and right-hand motor imagery trials. This protocol enables an evaluation of model generalization in the presence of intrasubject variability.

To enable a comparison of training strategies, we adopted an evaluation protocol across all experiments. Two classifiers were employed: Linear Discriminant Analysis (LDA) and Support Vector Machine (SVM). Their performance was averaged over the five folds to mitigate the impact of random sampling.

Given that the dataset was initially partitioned into individual subject training (80%) and testing (20%) subsets, the training portions from n subjects were concatenated to construct various multi-subject training schemes. Final evaluation was consistently conducted on the untouched 20% test sets, guaranteeing that no data leakage occurred during training.

4 Dataset Description

This study employs the IVa dataset from the BCI Competition III [4], which includes EEG recordings from five healthy subjects: aa, al, av, aw, and ay. The data was acquired using 118 electrodes positioned according to the international 10/20 system, with a sampling rate of 100 Hz.

The experimental paradigm involves three types of motor imagery tasks: left hand, right hand, and feet. For the purposes of this work, only trials corresponding to left- and right-hand motor imagery were selected. Each subject contributed a total of 280 trials, divided into a set of labeled training trials and a set of unlabeled testing trials, as summarized in Table 2. Notably, the number of training and testing trials varies across subjects.

Table 2. Trial distribution per subject of five healthy subjects: aa, al, av, aw and ay.

Subject	Training	Testing
	${f trials}$	$_{ m trials}$
1 (aa)	168	112
2 (al)	224	56
3 (av)	84	196
4 (aw)	56	224
5 (ay)	28	252

To ensure consistency and class balance across evaluations, the dataset was restructured to contain 224 labeled trials for training and 56 trials for testing for each subject, representing an 80%/20% train-test split. The correct labels for the test trials are available within the dataset, allowing for comprehensive evaluation.

Each EEG signal was segmented into epochs aligned with the motor imagery period. A 2-second time window was extracted from each trial, capturing the time interval during which the subject actively performed the motor imagery task.

5 Experimental Results

This section presents the experimental evaluation of various training strategies designed to explore intersubject generalization in MI-based EEG classification. First, we establish a baseline by training and testing models on each single subject (intrasubject evaluation). Then, we assess the generalization capacity of models trained under four different intersubject conditions: (1) using a single subject, (2) training on high-performing subjects (al, aw), (3) training on low-performing subjects (aa, av), and (4) training on all subjects (multisubject approach). All evaluations were performed using LDA and SVM classifiers, and results are reported in terms of accuracy, F1-score, and AUROC.

5.1 Intrasubject Evaluation

As a baseline, we trained and evaluated separate models on each single subject. Table 3 summarizes the results obtained with both classifiers. Subjects al, aw, and ay achieved high classification accuracy values, indicating strong motor imagery signals and model separability. Conversely, subjects aa and av yielded comparatively lower performance, highlighting individual differences and motivating further exploration of intersubject training frameworks.

Table 3. Classification performance per subject (Intrasubject Evaluation).

Subject		SVM			LDA	
zazjece		Precision	F1-score	Accuracy	Precision	F1-score
aa	85.00	84.85	84.85	82.85	82.16	83.12
al	97.85	99.31	97.81	98.21	100.00	98.16
av	75.35	73.43	76.11	74.64	73.76	75.01
aw	96.42	95.17	96.49	97.14	96.57	97.17
ay	95.71	94.20	95.87	95.71	93.34	95.86

5.2 Training on a Single Subject

In this configuration, models were trained using data from a single subject and evaluated on all others. This setup allows us to assess how well a model trained on one individual's EEG patterns generalizes across different users. Table 4 presents the accuracy results for SVM and LDA classifiers, respectively. Diagonal elements represent intrasubject performance, while off-diagonal values reflect intersubject generalization.

Eduardo V. Pérez-Hernández, Margarita Aviña-Corral, et al.

Table 4. Intersubject evaluation accuracy: Training on single subjects using SVM and LDA classifiers.

	Train	Test Subject				
Classifier	$\mathbf{Subject}$	aa	al	av	aw	ay
SVM	aa	85.00	68.21	60.35	47.85	50.00
S V IVI	al	50.71	97.85	54.64	50.00	50.00
	av	51.42	54.64	75.35	50.00	50.00
	$\mathbf{a}\mathbf{w}$	73.21	92.50	58.21	96.42	59.28
	ay	58.21	77.85	53.21	45.35	95.71
LDA	aa	82.85	79.64	53.21	63.92	49.64
LDA	al	66.42	98.21	55.35	61.42	50.00
	av	49.64	61.42	74.64	51.78	55.71
	$\mathbf{a}\mathbf{w}$	72.50	94.28	53.21	97.14	50.71
	ay	62.14	72.14	58.21	50.00	95.71

5.3 Training on High-Performing Subjects

To explore whether well-performing subjects can serve as effective training sources, we trained models using data from subjects al and aw, who previously showed good intrasubject results. This strategy assumes that clean and discriminative signals may provide strong generalization when applied to less reliable data. Table 5 reports classification metrics for this strategy.

Table 5. Performance with training on high-performing subjects (al, aw).

Subject		SVM			LDA	
Subject		Precision	F1-score	Accuracy	Precision	F1-score
aa	76.07	77.63	75.38	73.57	69.35	76.40
al	97.50	99.31	97.44	97.85	100.00	97.79
av	57.85	57.27	60.34	56.42	59.31	44.58
aw	95.71	94.01	95.84	97.14	99.31	97.04
ay	51.42	50.72	67.30	50.00	50.00	66.66

5.4 Training on Low Performing Subject

To evaluate the opposite strategy, we trained models exclusively on low-performing subjects (aa, av). The aim is to test whether models trained on inconsistent data can generalize to better-quality signals. Table 6 summarizes these results.

Table 6. Performance with training on low-performing subjects (aa, av).

Subject		SVM			LDA	
Subject		Precision	F1-score	Accuracy	Precision	F1-score
aa	84.64	84.42	82.85	82.50	82.62	82.60
al	62.85	57.55	72.83	65.35	60.62	74.75
av	77.85	75.53	78.65	79.64	81.64	78.65
aw	50.71	50.37	66.99	54.64	52.46	68.47
ay	51.78	50.98	67.51	61.07	58.78	57.85

5.5 Multisubject Approach

Finally, we trained models using the labeled training sets (80%) from all five subjects and evaluated them on the remaining 20% for each individual. This approach seeks to maximize training diversity and capture general patterns across individuals. Table 7 presents the results. Notably, the multisubject strategy achieved a mean accuracy of 88.14%, only 2.5% points below the intrasubject baseline, while eliminating the need for subject-specific calibration.

Table 7. Performance using the multisubject training strategy.

Subject	\mathbf{SVM}			LDA			
Bubject		Precision	F1-score	Accuracy	Precision	F1-score	
aa	84.64	91.20	83.37	80.00	81.70	79.92	
al	97.50	99.31	97.44	95.00	98.62	94.76	
av	73.57	75.70	71.87	70.00	79.35	63.25	
aw	95.00	92.59	95.13	90.35	87.21	90.80	
ay	90.00	89.12	90.03	79.64	73.26	82.27	

5.6 Discussion

Table 8 presents a comparison of classification performance across different training strategies. The third column shows the accuracy obtained when training and testing a subject-specific model (intrasubject scenario). This strategy consistently achieved the highest average accuracy—90.06% with SVM and 89.71% with LDA—highlighting the benefits of subject-specific characteristics in the classification model training.

The Multisubject strategy, where the model is trained on the combined data from all available subjects and tested on a held-out individual, yielded slightly lower but competitive performance (88.14% for SVM and 82.99% for LDA). This strategy demonstrates strong generalization capabilities and serves as a viable solution when subject-specific data is unavailable.

The fifth column, the accuracy results for classification models trained with high-performing subjects (al, aw), are presented. Column six then shows the results from training with low-performing subjects (aa, av). Classification models trained on high-performing subjects achieved moderate average accuracy (75.71% with SVM and 74.99% with LDA), demonstrating reasonable generalization to other individuals with similar signal characteristics. Conversely, training with low-performing subjects resulted in significant performance degradation, particularly for LDA (down to 68.64%).

Table 8. Classification accuracy (%) for different training configurations using SVM and LDA.

Classifier		Single ct Subject	Multisubject	Intrasubject (al, aw)	Intrasubject (aa, av)
	aa	85.00	84.64	76.07	84.64
	al	97.85	97.50	97.50	62.85
SVM	av	75.35	73.57	57.85	77.85
	aw	96.42	95.00	95.71	50.71
	ay	95.71	90.00	51.42	51.78
	Avg.	90.06	88.14	75.71	65.56
	aa	82.85	80.00	73.57	82.50
	al	98.21	95.00	97.85	65.35
LDA	av	74.64	70.00	56.42	79.64
	aw	97.14	90.35	97.14	54.64
	ay	95.71	79.64	50.00	61.07
	Avg.	89.71	82.99	74.99	68.64

These results demonstrate that classification models trained on data from high-performing subjects achieve reasonable generalization to other individuals, particularly those with similar signal quality. However, performance degrades significantly when the training set is limited to low-performing subjects, highlighting the importance of subject diversity and signal quality in multisubject training scenarios. Notably, training with all subjects leads to a more balanced performance across individuals, approaching the accuracy of subject-specific models in some cases, while enabling broader generalization.

6 Conclusions

This work evaluated multiple training configurations for motor imagery classification under subject-independent conditions. The multisubject strategy achieved an average accuracy of 88.14%, only 2.5% points below the subject-specific (intrasubject) strategy models. This small gap is significant considering that the multisubject model operates without individual calibration, offering a more scalable and user-friendly alternative for real-world BCI systems.

Furthermore, the use of only three CSP components per sub-band preserved a low-dimensional feature space, which supports both computational efficiency and practical deployment, particularly in resource-constrained or real-time applications.

The results also show that classification models (LDA and SVM) trained exclusively on high-performing subjects retain strong performance for those same individuals but fail to generalize effectively to others. Likewise, classification models trained on low-performing subjects replicate their limited performance but show poor generalization to users with better-quality signals. These findings reinforce the idea that inter-subject variability—a significant challenge in EEG-based BCI—is best addressed through diversity in the training set.

For future work, we plan to investigate transfer learning techniques by integrating external EEG datasets that follow similar motor imagery paradigms. The goal is to exploit cross-dataset and cross-subject knowledge to enhance generalization further. By doing so, we aim to reduce calibration requirements for new users and improve performance in real-world applications.

Acknowledgments. The first three authors, wish to express their gratitude for the graduate scholarships granted by Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI), Mexico. These grants have enabled them to conduct the research presented in this work.

References

- Ang, K.K., Chin, Z.Y., Zhang, H., Guan, C.: Filter bank common spatial pattern (fbcsp) in brain-computer interface. In: 2008 IEEE International Joint Conference on Neural Networks (IEEE World Congress on Computational Intelligence). pp. 2390–2397 (2008). https://doi.org/10.1109/IJCNN.2008.4634130
- Antonakakis, M., Schrader, S., Wollbrink, A., Oostenveld, R., Rampp, S., Haueisen, J., Wolters, C.H.: Inter-subject variability of skull conductivity and thickness in calibrated realistic head models. NeuroImage 223, 117353 (2020). https://doi.org/10.1016/j.neuroimage.2020.117353
- 3. Becker, S., Dhindsa, K., Mousapour, L., Al Dabagh, Y.: Bci illiteracy: It's us, not them. optimizing bcis for individual brains. In: 2022 10th International Winter Conference on Brain-Computer Interface (BCI). pp. 1–3 (2022). https://doi.org/10.1109/BCI53720.2022.9735007
- Blankertz, B., Muller, K.R., Krusienski, D.J., Schalk, G., Wolpaw, J.R., Schlogl, A., Pfurtscheller, G., Millan, J.R., Schroder, M., Birbaumer, N.: The bci competition iii: Validating alternative approaches to actual bci problems. IEEE transactions on neural systems and rehabilitation engineering 14(2), 153–159 (2006)
- 5. Ghane, P., Zarnaghinaghsh, N., Braga-Neto, U.: Comparison of classification algorithms towards subject-specific and subject-independent bci. In: 2021 9th International Winter Conference on Brain-Computer Interface (BCI). pp. 1–6 (2021). https://doi.org/10.1109/BCI51272.2021.9385339
- Kabir, M.H., Akhtar, N.I., Tasnim, N., Miah, A.S.M., Lee, H.S., Jang, S.W., Shin, J.: Exploring feature selection and classification techniques to improve the performance of an electroencephalography-based motor imagery brain-computer in-

- terface system. Sensors $\mathbf{24}(15)$, 4989 (2024). https://doi.org/10.3390/s24154989, https://doi.org/10.3390/s24154989
- Petrov, M., Atyabi, A.: Enhancing mi-bci classification with subject-specific spatial evolutionary optimization and transfer learning. In: 2024 IEEE International Conference on Systems, Man, and Cybernetics (SMC). pp. 4770–4777 (2024). https://doi.org/10.1109/SMC54092.2024.10830968
- 8. Saha, S., Ahmed, K.I.U., Mostafa, R., Hadjileontiadis, L., Khandoker, A.: Evidence of variabilities in eeg dynamics during motor imagery-based multiclass brain-computer interface. IEEE Transactions on Neural Systems and Rehabilitation Engineering 26(2), 371–382 (2018). https://doi.org/10.1109/TNSRE.2017.2778178
- Saha, S., Baumert, M.: Discrepancy between inter- and intra-subject variability in eeg-based motor imagery brain-computer interface. Frontiers in Neuroscience 14, 1122661 (2020). https://doi.org/10.3389/fnins.2023.1122661
- Shiam, A.A., Hassan, K.M., Islam, M.R., Almassri, A.M.M., Wagatsuma, H., Molla, M.K.I.: Motor imagery classification using effective channel selection of multichannel eeg. Brain Sciences 14(5) (2024). https://doi.org/10.3390/brainsci14050462, https://www.mdpi.com/2076-3425/14/5/462
- Shuqfa, Z., Lakas, A.: Towards user-centered design for motor imagery brain-computer interface: From mi-bci illiteracy to mi-bci unfamiliarity. In: 2024 IEEE/ACM International Conference on Big Data Computing, Applications and Technologies (BDCAT). pp. 270–275 (2024). https://doi.org/10.1109/BDCAT63179.2024.00050
- Smith, M.E., Gevins, A.: Neurophysiologic monitoring of mental workload and fatigue during operation of a flight simulator. Proceedings of the Human Factors and Ergonomics Society Annual Meeting 49(1), 117–121 (2005). https://doi.org/10.1177/154193120504900127
- Tao, L., Cao, T., Wang, Q., Liu, D., Sun, J.: Distribution adaptation and classification framework based on multiple kernel learning for motor imagery bci illiteracy. Sensors 22(17) (2022). https://doi.org/10.3390/s22176572, https://www.mdpi.com/1424-8220/22/17/6572
- 14. Wang, T., Du, S., Dong, E.: A novel method to reduce the motor imagery bci illiteracy. Medical & Biological Engineering & Computing $\bf 59(10)$, 2205-2217 (2021). https://doi.org/10.1007/s11517-021-02449-0
- Zaremba, T., Atyabi, A.: Cross-subject & cross-dataset subject transfer in motor imagery bci systems. In: 2022 International Joint Conference on Neural Networks (IJCNN). pp. 1–8 (2022). https://doi.org/10.1109/IJCNN55064.2022.9891904
- Zhang, R., Xu, P., Liu, T., Zhang, Y., Guo, L., Li, P., Yao, D.: Local temporal correlation common spatial patterns for single trial eeg classification during motor imagery. Computational and Mathematical Methods in Medicine 2013, 591216 (2013). https://doi.org/10.1155/2013/591216, https://doi.org/10.1155/2013/591216