Evaluation of algorithms for correction of transcranial magnetic stimulation-induced artifacts in electroencephalograms

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Abstract

Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) is widely used to study the reactivity and connectivity of brain regions for clinical or research purposes. The electromagnetic pulse of the TMS device generates at the instant of administration an artifact of large amplitude and a duration up to tens of milliseconds that overlaps with brain activity. Methods for TMS artifact correction have been developed to remove the artifact and recover the underlying, immediate response of the cerebral cortex to the magnetic stimulus. In this study, four such algorithms are evaluated. Since there is no ground truth for the masked brain activity, pilot data formed from the superposition of the isolated TMS artifact on EEG brain activity are used to evaluate the performance of the algorithms. Different scenarios of TMS-EEG experiments are considered for the evaluation: TMS at resting state, TMS inducing epileptiform discharges, and TMS administered during epileptiform discharges. We show that a proposed gap filling method is able to reproduce qualitative characteristics and, in many cases, closely resemble the hidden EEG signal. Finally, shortcomings of the TMS correction algorithms as well as the pilot data approach are discussed.

Keywords

Transcranial magnetic stimulation · Electroencephalography · Artifact correction · Delay embedding

1 Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive method for brain stimulation with electromagnetic pulses delivered via stimulation coils [3]. The pulse has short duration (<1 ms) and peak amplitude up to 3 Tesla. Short duration-high frequency-induced electric currents are able to penetrate the cell membranes and depolarize pyramidal cells and interneurons. Depending on the equipment, the depth of the stimulation can be up to 6 cm [32, 33]. The reaction of the cortex can be recorded by combining TMS and electroencephalography (TMS-EEG) [15] and depends on different factors such as the precise site of stimulation [25], the direction of the coil, the type of the coil [40], the power of the pulse [26, 47], the form of the pulse [20], the state of the brain [43], and the level of consciousness [36]. The reaction occurs first at the stimulation area and then spreads to more distant areas as the activation is transmitted along existing neural pathways [16]. Thus, TMS-EEG is an excellent tool to measure connectivity between distinct brain areas and reactivity to a specific stimulation pattern [15]. TMS-EEG has been utilized for diagnostic [24] and therapeutic purposes [30]. In addition, TMS-EEG responses, which are characterized by reproducibility and reliability [5, 22, 31], can be used as a monitoring tool for therapeutic interventions, i.e., for instance for evaluating the effects of repetitive TMS (rTMS), which acts as a modulator of neural activation and leads to reorganization of cortical connections [15].

A key issue in the preprocessing of TMS-EEG recordings is the correction of artifacts generated by the electromagnetic pulse of the TMS device and the unintended activation of physiological systems other than the brain per se (muscle and trigeminal nerve activation, eye movements) [15, 40]. The artifact is observed in the EEG as fluctuations of several orders of magnitude larger than electrophysiological activity.

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Though several techniques have been suggested and are in use for reducing this effect, e.g., a sample-and-hold circuit [49], improved EEG amplifiers such as direct current coupled amplifiers [6, 17, 48], puncturing of the skin [19], and use of active EEG electrodes [9], the remaining TMS-induced artifact in the EEG is relatively large and has a duration up to 20 ms. Thus, early TMS evoked potentials (i.e., at a latency ≤ 20 ms) are masked by the TMS-induced artifact. Complete removal from the analysis of channels heavily contaminated by the artifact would mean that valuable information would be lost (since these channels would be exactly the ones close to the stimulation site), e.g., this could lead to a systematic error in source estimation [32].

The analysis of TMS-EEG requires the offline correction of the TMS-induced artifact, termed simply TMS artifact. Blind source separation methods have been proposed to separate cortical and non-cortical sources and thus remove the TMS artifacts, such as techniques based on independent component analysis (ICA) [15, 27, 41] and principal component analysis (PCA) [11, 32, 45], and the so-called signal-space projection [34, 35]. ICA-based TMS artifact correction algorithms have been built in the FieldTrip toolbox [37], as well as the two recent Matlab modules for TMS-EEG processing, TMSEEG [1] and TESA [42]. In a different approach, rather than attempting to identify and remove the artifact from the signal, the whole signal affected by the artifact is treated as corrupted and considered as a gap to be filled by an interpolation method, such as linear or cubic interpolation [4, 46]. A more advanced interpolation approach is proposed in [23], filling the gap from the weighted forward-backward prediction of a local state space model.

The immediate cortex activity evoked by the TMS is not known as it is masked by the TMS artifact, and thus there is no ground truth to be used as reference for the evaluation of TMS artifact correction algorithms. For the evaluation of the algorithms, qualitative characteristics of the corrected signal are used, e.g., based on its time-frequency representation [18].

In this study, we evaluate four of the artifact correction algorithms discussed above. The first two identify and remove the artifact from the signal, i.e., the FastICA algorithm [12] and the separation algorithm making use of PCA and the source to sensor forward model, termed here as the PCA model [32]. The last two, i.e., the advanced gap filling method in [23] and standard interpolation methods, discard the recording near the artifact and try to fill the resulting gap. For the evaluation, we first estimate the artifact from TMS-EEG recordings at rest, obtained by averaging over several iterations of stimulation. The artifact is then added to three types of high-density EEG signals: resting EEG, EEG at the onset of an epileptiform discharge (onset ED), and EEG in the course of an epileptiform discharge (mid-ED). The correction algorithms are applied to the resulting pilot signals. The signal derived from the superposition of the TMS artifact and the initial EEG signal lacks the possible interplay of artifact and underlying neuronal activity. Nevertheless, it allows using the initial EEG as a reference to evaluate the corrective capacity of each algorithm.

2 Methods

The structure of the study is as follows. First, the four TMS artifact correction methods are discussed, and then the procedure for generating pilot EEG signals as well as the estimation and evaluation of the correction methods are presented.

2.1 TMS-induced artifact correction methods

2.1.1 FastICA

FastICA is a time-efficient algorithm implementing independent component analysis (ICA) [12, 13] (for a more general description of ICA and relative illustrations look at [14]). It has been applied to correct TMS artifacts in EEG recordings in several studies [15, 27, 41]. Possible preprocessing steps are data centering, whitening, and dimensionality reduction, the latter being done by PCA in FastICA. The rationale of ICA is to separate independent sources being mixed in the observed multichannel EEG signal [8]. For this, statistical independence of the independent components (ICs) is achieved using a procedure that maximizes non-Gaussianity of the estimated sources. In the case of TMS-EEG, it is hypothesized that the artifactual sources are independent from the neuronal sources, and thus can be separated by ICA (i.e., some of the ICs will be strictly artifactual and the rest strictly neuronal). FastICA uses the so-called fast fixed-point algorithm to run faster and projection pursuit to find the ICs. The algorithm can be configured to produce the ICs one at a time (deflation approach) or converge to the full set of ICs at once (symmetric approach).

Statistical independence is a very strong condition in ICA and requires an infinite length of data to be verified. An acceptable lower limit for the length of a signal of N channels is 3N². For shorter EEG signals, PCA is used to reduce the dimension N. ICA generally outputs the ICs in random order. As FastICA uses PCA for preprocessing, ICs are given in decreasing variance (power) order and since the artifact has much larger variability than the physiological signal, the ICs corresponding to the artifact come first. Specifically, recognition can be done in two ways. Firstly, by observing the ICs themselves, and looking for large fluctuations at the time of the artifact that decay to zero when there is no artifact. These ICs can be identified easily, by centering each IC, taking the absolute value and deciding for rejection according to a given threshold. The reconstructed artifact-free signal is then obtained by the remaining ICs. The second way is more complex and is based on the observation of the topography matrix that
represents the spatial distribution of each IC. Knowing the stimulation site, the distribution of the artifact on the scalp can be estimated, identified, and the artifact finally removed. ICA and FastICA implementations are standard in EEG processing software packages, such as EEGLAB [7] and Fieldtrip [37].

2.1.2 PCA model

Various PCA-based methods have been proposed to correct TMS artifacts in EEG recordings [11, 32, 45] (for a tutorial on PCA including illustrations, see [44]). The method introduced in [32] attempts to separate the neuronal activity signal from artifact activity. Unlike ICA, it makes no assumption about spatial or temporal independence of neuronal and artifact activities. Instead, it relies on the construction of a source model consisting of topographies of neuronal and artifact sources. The source model and a linear inverse operator decompose the data into a linear combination of artifact and neuronal signals and the artifact signals are then subtracted from the data. The model for the neuronal topographies requires that the head model and the electrode positions are known. Activation of a dipole with a known position produces a specific topography of activity at the electrode positions on the head surface. The information of this linear and constant (over time) activation relationship is forwardly produced and stored in the lead field matrix. The artifact topographies are obtained from a PCA decomposition of the averaged artifact using the minimum possible number of sources. For TMS–EEG data, it is the early signal (<20 ms) that primarily represents the TMS artifact.

If the topography of the neuronal sources is known in advance, study-specific models can be used. However, this is not the case in general. Therefore, this algorithm uses a two-step iterative procedure to approximately model the neuronal sources. In the first step, neuronal activity is represented by a surrogate model, with 15 sources distributed around all major cortical regions. This model is capable of approximately reproducing any recorded activity on the surface, with an appropriate activation of each source. The artifact is corrected using the model derived by PCA and the surrogate neuronal model, and the corrected signal is used to build a new, study-specific model for the neuronal sources. In the second step, the correction is done using this improved model of neuronal sources in synergy with the lead field matrix for the artifact sources already calculated. So, eventually the positions of the sources are not forced to be those of the surrogate model.

The quality of separation of neuronal sources depends on the model of artifact sources, and vice versa [32]. This poses a problem, as an exact model for one cannot be produced in the presence of the other. The PCA model method [32] is included in the SPM package [10].

2.1.3 Gap filling

This is a data-driven interpolation method adapted from [38]. It is based on discarding the signal with artifact, treating it as totally corrupted and replacing it with a gap, and then filling the gap with an appropriate data-driven model (see Fig. 1). The window of the gap depends on the type of artifact, and in [23] the segment [−10, 30] ms around the TMS onset was replaced with a gap. The interpolation model proposed in [23] is a local state space model stemming from the nonlinear analysis of time series under the perspective of dynamical systems theory [21]. The hypothesis is that there is a dynamical system underlying the signal from the electrode, and the missing signal can be reconstructed by a model of this dynamical system extrapolating it forwards and backwards in time from the beginning and end of the gap, respectively.

The model requires the reconstruction of the state space from the measurements of the variable $x_t$, where $x$ is the scalp potential measured at an electrode and $t$ is the time index (multiple of the sampling time). The point at time $t$ in the reconstructed state space of dimension $m$ is $x_{t} = [x_t, x_{t-\tau}, \ldots, x_{t-(m-1)\tau}]$, where $\tau$ is the time delay parameter. In [23], an embedding dimension of $m = 50$ and delay $\tau = 1$ were selected, and the number of neighbors $k$ defining the neighborhood around $x_{t}$ for which the model is valid was set to $k = 2$. The prediction of the next observation $x_{t+1}$ is given by the average of the one-time ahead observations of the $k = 2$ nearest neighbors of $x_{t}$. The prediction is iterated for the target point $x_{t+1}$ formed in the same way and given the predicted observation $x_{t+1}$, and until the whole missing segment is estimated, covering the interval [−10, 30] ms with reference to the stimulation time point.

A very small $k = 2$ is used to preserve the local approximation in a very high dimensional space ($m = 50$), and $k = 1$ is avoided to preclude predicting reoccurring segments [38]. We let $\tau = 1$ and $m = 50$ to include all details of the fluctuating signal of 50 time units in the search for similar preceding segments (nearest neighbors). For the prediction of the missing segment, the nearest neighbors are sought in the last 210 ms, i.e., the interval [−220, −10] ms (forward prediction). The same missing segment is predicted again by shifting the direction of time and using the interval [30, 280] ms to search for nearest neighbors (backward prediction). The forward and backward predictions for each predicted observation in [−10, 30] ms are weighted and the weights change linearly going from 1 to 0 for the forward prediction and from 0 to 1 for the backward prediction as the prediction time goes from −10 to 30 ms, so that the sum of the weights always gives 1. There may be considerable changes in the signal before and after the gap, and by this weighting scheme the algorithm adjusts the gap filling to the closest state, before or after the gap [23].
2.1.4 Interpolation

Standard interpolation methods are used for TMS artifact correction in EEG recordings in EEG processing software packages, such as EEGLAB [7] and Fieldtrip [37]. These methods reject the contaminated signal similarly to the gap filling method, but they are much simpler conceptually, and not tuned to the specifics of the problem. Thus, they will primarily serve as a benchmark for the gap filling method.

2.2 Data

The TMS-EEG data were recorded at the Lab of Clinical Neurophysiology, the Medical School of Aristotle University of Thessaloniki, from a 37-year-old female patient with Juvenile Absence Epilepsy, a subtype of Genetic Generalized Epilepsy. Recordings were performed in an electrically shielded room according to TMS-EEG methodological guidelines [15]. The EEG recordings of 60 channels in 10-10 montage were recorded with a TMS compatible EEG system (eXimia, Nexstim Ltd.), at a sampling rate of 1450 Hz and bandpass filtered between 0.1 and 500 Hz. Brain stimulation was performed with a MagPro X100 stimulator (MagVenture A/S, Farum, Denmark) with a circular coil centered over the vertex. In order to reduce the TMS-induced artifact, the EEG amplifier was temporarily blocked from 100 μs before to 2 ms after the TMS pulse by a sample-and-hold circuitry. For the main part of study, we employed a circular coil. We did not use neuronavigational techniques throughout the experiments. The paradigm employed was intended to abort TMS-induced EDs. To this end, a pair of TMS stimuli at the epileptogenic threshold (defined in [24]) was followed by a train of five TMS pulses at a frequency of 4 Hz. The stimulation site was Cz. Still, the TMS administration gives rise to high amplitude sharp fluctuations up to 20 ms post-TMS, masking the brain activity in the EEG.

Additional recordings with stimulation from a figure-of-8 coil were included for comparison purposes. In this case, we used a figure-of-8 coil, optimally localized and oriented over the left motor hand area (target muscle = right first dorsal interosseous), and we employed an identical stimulation paradigm, as above (i.e., a pair of pulses at 4 Hz and 140% motor threshold, assessed with an adaptive threshold technique [2], followed after 1 s by 5 TMS pulses at the same frequency and intensity). The data were processed in Matlab R2012a and R2016a (MathWorks Matlab, Natick, Massachusetts, USA) using the FastICA 2.5 (Aapo Hyvärinen, Gatsby Unit, University College London) and SPM8 (Wellcome Centre for Human Neuroimaging, University College London) packages.

The sampling frequency and the cutoff frequency of the pre-filter affect the shape of the TMS artifact. The TMS artifact fluctuations have sharp slopes and thus contain considerable power in higher frequencies (> 100 Hz). However, if a slow sampling frequency, or equivalently a low cutoff frequency is used, the artifact is reduced in power but also spread over time. To avoid this, a sampling frequency at least five times the maximum frequency in the artifact spectrum and a
cutoff frequency not below 1000 Hz are recommended [48]. On the other hand, the stretch in time could be corrected since a big part of the artifact power will be gone by the filtering that caused the stretch. The TMS artifact correction algorithms were applied to the raw EEG without any filtering. Filtering before applying the correction algorithms was also tested. In this case, a bandpass filter at 1–100 Hz was used, since the study is not limited to a particular brain rhythm.

2.3 Artifact estimation and pilot signals

To estimate the TMS artifact, the average is taken over nine TMS epochs spanning the time interval [−10, 30] ms with reference to the stimulation onset. All TMS epochs contain the first TMS pulse in a train of TMS pulses, repeated throughout a recording at rest. Each train comprises two TMS pulses at 4 Hz frequency followed after 1 s by five TMS pulses at the same frequency, as shown in Fig. 2. Note that the subsequent TMS pulses in the same TMS train may contain effects of the previous TMS pulse [39], and therefore only the first TMS in the train is considered. The artifact differs across channels, so we only average across epochs to receive one averaged artifact for each channel.

The rationale behind this approach for artifact estimation is as follows. The immediate neuronal reaction to the stimulation (TMS-evoked activity) is likely to be similar across epochs and much smaller than the artifact. Any other brain activity (spontaneous EEG activity) is expressed as fluctuations around the baseline in the EEG signal. These fluctuations are not expected to contain any systematic pattern in the interval of the TMS artifact, and thus they will cancel out when averaging across epochs. Finally, only the signals of interest, i.e., the TMS artifact and any neuronal reaction that it systematically induces, will be kept after averaging. Note that any such consistent neuronal reaction will still be unrelated to the underlying pilot signal that we are using. Thus, this neuronal reaction can still be considered as part of the artifact to be removed, in this setting. Since it is also much smaller than the TMS artifact, it will not affect the assessment of the performance of the algorithms.

The artifact in our measurements appears within the first 30 ms after the pulse, but after estimating it with the aforementioned method, we find that at its margins the signal amplitude is still about three times larger than that of the EEG at rest. To avoid discontinuities after the artifact is added to the pilot signals, which will introduce high frequencies in the signal and affect filtering, the calculated artifact is multiplied by a steep Tukey window to fix its marginal values at −10 and 30 ms to zero.

The average TMS artifact spanning a time interval of 40 ms, i.e., the period of interest [−10, 30] ms, is added to EEG signals of three types: (a) at rest, (b) in the beginning of an epileptiform discharge (onset ED), and (c) within the epileptiform discharge (mid-ED). The selection of the types (b) and (c) is motivated by settings that have occurred in studies of our group, namely induction of ED by TMS for (b) [24, 29], and abortion of ED by TMS for (c) [23, 28]. The length of each EEG signal on which the TMS artifact is added is 460 ms (669 ms).

Fig. 2 An EEG segment containing a train of TMS pulses, i.e., a pattern of two TMS pulses at 4 Hz followed after 1 s by five TMS pulses at the same frequency. This pattern was used throughout the experiments.
observations) to account for practical constraints, where the TMS onset is at 210 ms to allow for baseline activity estimation prior to TMS administration and the 250 ms after TMS is in accordance with repetitive TMS (rTMS) at a frequency of 4 Hz. Five trials across all channels were included for conditions (a) and (c), and a single trial for condition (b). The number of trials included per condition was kept constant when other parameters (e.g., EEG signal length) were varied.

3 Results

In this section, we assess the quality of TMS artifact correction with reference to the true EEG for each of the four studied methods.

3.1 FastICA

3.1.1 Resting EEG

The rationale of the FastICA method is to identify and remove ICs corresponding to the TMS artifact. Initially, the method was applied to all channels except Cz and without PCA dimension reduction and gave 59 ICs. An example of five randomly chosen EEG signals and ICs is shown in Fig. 3a, d, respectively.

It appears that many ICs exhibit peaks of varying amplitude at the time of TMS and thus it is hard to identify a few ICs containing the TMS artifact and others containing only brain activity. We set a threshold for the amplitude to identify the ICs having a strong TMS artifact component, as shown in Fig. 3e. This threshold was found by simple visual inspection of the ICs and was set to 5 μV for TMS during resting state and 6.5 μV otherwise, since these values always separated ICs with a strong component during the TMS pulse. Twenty-eight ICs were removed, and the 31 remaining ICs having amplitude smaller than the threshold, 3 of which are shown in Fig. 3f, seem to lack any activity at the time of TMS. The 59 EEG signals reconstructed from the 31 ICs of low amplitude, shown in Fig. 3b, also do not exhibit any neuronal activity at the time window of the TMS artifact and display merely a straight line. On the other hand, the discarded ICs of large amplitude do not go to zero at times outside the TMS window, indicating that they carry some information about neuronal activity as well. Based on these findings, we conclude that the artifact cannot be isolated from the neuronal activity in any subset of ICs. As a result, the reconstructed EEG signals exhibit significantly deformed neuronal activity outside the...
TMS window, as can be seen from the large difference in EEG before and after the artifact correction in times outside the TMS window, shown in Fig. 3c.

We apply FastICA employing PCA dimension reduction using the “symmetric” approach and retain 15 ICs, which is the maximum that can be obtained for waveforms of 669 observations according to the $3N^2$ rule. We apply the same thresholding resulting to only two ICs of low amplitude (i.e., 13 ICs are removed) and thus the 59 reconstructed EEG signals from these 2 ICs are heavily correlated and look very similar. The very large amplitude of the TMS artifact results in almost all ICs being required to describe its variability, leaving only few ICs (two here) to be more representative of the neuronal activity. The opposite would be desired, i.e., a few ICs to represent the TMS artifact and be discarded, but the algorithm cannot achieve this.

In an attempt to assess the effectiveness of the algorithm if the TMS artifact would not have such large amplitude, we selected for TMS artifact correction a subset of 28 EEG channels having the smallest amplitude of TMS artifact, excluding some irrelevant channels in perimeter areas, as well as nearby channels with an almost identical artifact, so as to include channels from all scalp regions. We applied PCA dimension reduction to 15 ICs using the “symmetric” approach and after thresholding we obtained three ICs (i.e., 12 ICs were removed). The “deflation” approach gave 4 ICs (11 ICs removed). In both cases, the TMS artifact was not successfully isolated, and a great deal of neuronal activity outside of the TMS window was lost.

In an effort to obtain more ICs without TMS artifact components, EEG channels were further reduced to 18 channels relaxing the criterion of having channels from all scalp regions. Again, using PCA dimension reduction to 15 ICs, the symmetric approach and thresholding, we obtained 4 ICs (11 ICs were removed) and the reconstructed EEG signals were distinctly different at times outside the TMS artifact, indicating once again that the method is unable to separate the neuronal activity from the TMS artifact.

In a last attempt to find positive results with this method, we first filtered the EEG signals with a low pass filter at 100 Hz. The benefit of this is that the TMS artifact amplitude is reduced as it contains frequencies higher than 100 Hz, while neuronal activity is not altered as it is mostly found in frequencies lower than 100 Hz. Also, the filtering of the background noise at high frequencies increases the efficiency of the PCA dimension reduction. However, the results did not improve. FastICA did not converge when 18 channels were selected and the reduced dimension was set to 15, and therefore no dimension reduction was applied. When the “deflation” approach was used, the reconstructed EEG signals (removing eight ICs and keeping the 10 ICs without artifactual signal) again differed significantly from the original ones outside the time window of the TMS artifact.

3.1.2 Epileptic EEG

So far, we have seen results from resting EEG. During an epileptic seizure, EEG is much larger in amplitude, which makes the difference between neuronal and artifact signals less prevalent. As seen in Fig. 4a for the case of 18 EEG signals, large peaks outside the [0, 40] ms window, corresponding to the epileptic activity, are reproduced satisfactorily by FastICA (PCA dimension reduction set to 15 ICs and “deflation” approach was used, as the “symmetric” approach did not converge, 7 non-artifactual ICs were kept, 8 ICs removed). These large epileptic fluctuations are represented well by some ICs. However, the error amplitude remains at the order of neuronal activity at rest. Moreover, as shown in Fig. 4b, the correction of the TMS artifact leads to a high-frequency oscillation of smaller amplitude in the artifact window because the preserved ICs that correspond primarily to neuronal signals contain also some of the variance of the artifact. These results are similar to the ones obtained with the same procedure (the “symmetric” approach is shown here since it converged) on the onset-ED EEG signal type, as can be seen in Fig. 4c, d (six non-artifactual ICs were kept, nine ICs removed).

3.1.3 Figure-of-8 coil

Finally, FastICA was applied to data from the figure-of-8 coil. The resulting artifact is comparatively small, and FastICA performs better, as expected. Figure 5 shows results from resting EEG. After dimension reduction to 15 ICs, only 3 ICs are artifactual (12 non-artifactual). This is much better than before, but still good separation with the resting EEG signal is not achieved, and neuronal activity outside of the TMS window is lost. Similar results were obtained for the onset-ED and mid-ED signals.

3.2 PCA model

3.2.1 Resting EEG

The application of FastICA showed that the TMS artifact has large amplitude varying across channels, so that the artifact cannot be captured by a small subset of ICs. The same is expected to apply for PCA. The PCA model method uses PCA expecting that the artifact will be expressed only in the first few principal components. This does not seem to be the case, as confirmed by our results on the set of 55 channels (coordinates for 4 of the electrodes were not available). For the resting state EEG signals, the method only reduces the TMS artifact amplitude to a lesser or larger degree (Fig. 6a, b, respectively). The reduction of the TMS artifact comes also at the cost of distortion of the signal outside the TMS artifact window.
In an attempt to modify the setting in favor of the PCA model, we selected 18 of the 55 channels having the lowest TMS artifact amplitude and similar shape. The results for resting state (Fig. 6c) were slightly better as there was a better suppression of the artifact, with only small increases in a few channels, but the same issues persisted.

3.2.2 Epileptic EEG

The distortion in the corrected signals was larger for the other two scenarios of mid-ED and onset-ED EEG, and the amplitude of the TMS artifact was reduced less compared to the resting state (Fig. 6d). This is also attributed to the different intensity and shape of the TMS artifact across the 55 channels.

3.2.3 Figure-of-8 coil

Finally, the PCA model method was applied to data from the figure-of-8 coil. Even though the artifact is smaller, the method does not perform substantially better. Figure 7 shows example results from resting and mid-ED EEG. We observe that the artifact is suppressed, but so is the neuronal activity outside of the TMS window, similarly to what was seen before. We also observe that sometimes an artifact of opposite polarity emerged (see Fig. 7a). Similar results were obtained for the onset-ED signals. We conclude that the PCA model method is not able to separate and suppress the artifact adequately.

3.3 Gap filling

3.3.1 Resting EEG

In contrast to FastICA and the PCA model artifact correction, the gap filling method gave satisfactory results on resting state EEG signals, in terms of replacing the artifactual signal with a more realistic, EEG-like signal. In general, the oscillations of the neuronal activity masked by the TMS artifact were closely

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**Fig. 4** FastICA results for 18 channels and dimension reduction to 15 for the TMS administration during ED (mid-ED EEG) with the TMS artifact in (a) and with the TMS artifact corrected in (b), and for the TMS administration inducing ED (onset ED EEG) with the TMS artifact in (c) and with the TMS artifact corrected in (d).
approximated, in cases succeeding also to be in phase (Fig. 8a) and in other cases with a time lag (Fig. 8c). Less frequently, the method failed to capture the original oscillations at a lesser or larger extent (Fig. 8e). To show the correction more clearly in the three representative examples in Fig. 8, the same signals are shown after low-pass filtering at 100 Hz in Fig. 8b, d, f, respectively.

### 3.3.2 Epileptic EEG

The results from artifact correction in mid-ED signals showed that unlike the case of resting EEG, the corrected signals may deviate in shape substantially from the original ones. While in some cases the corrected signal has similar shape to the original one (Fig. 9a), in many other cases peaks appear in the corrected signal not existing in the original one (Fig. 9b). This is to be expected, as seizures last for a few seconds and the large amplitude oscillations have a period of about 1/4 of a second, being half the time window of the training set for the gap filling model. Even when the deviation appears to be relatively small (Fig. 9a), it is still large compared to the resting EEG case. Thus, the artifact correction cannot approximate the original EEG signal but nevertheless the produced signal by the gap filling method contains oscillations that could be considered as part of the ED activity.

The onset-ED signal has similar features with the mid-ED signal (slow waves) at the part after the magnetic stimulus and therefore it is likewise difficult to retrieve the EEG signal masked by the TMS artifact. However, as the first part of the recording before the TMS is at rest, the deviation from the true EEG signal was smaller than for the mid-ED signal, as shown in a representative example in Fig. 9c.

### 3.3.3 Figure-of-8 coil

The application of the gap filling method on data from the figure-of-8 coil yielded identical results, since we elected to keep the size of the correction window constant even though the artifact is less extended in time. The size of the artifact does not affect the algorithm, only the temporal extent of it does.

### 3.3.4 Pre-filtering effects

Filtering the TMS-corrupted EEG signal prior to applying the gap filling method could possibly improve the predictability of the method. However, filtering increases the duration of the artifact. As shown in Fig. 9d, the TMS artifact after filtering extends in both edges and its duration goes from 40 ms before filtering to about 70 ms after filtering. Thus, the gap to be filled by the forward-backward prediction method is longer and the overall approximation of the true signal is worse, as shown in the example of the filtered signal in Fig. 9d, to be compared to the raw signal in Fig. 8a, b. The increase in TMS
artifact duration with filtering depends on the artifact amplitude. For the 100 Hz cutoff filtering, the power of the artifact is reduced by a factor of about 1.4. Using a larger cutoff results in smaller power reduction and artifact duration increase, e.g., for 200 Hz cutoff the duration is approximately 60 ms and the correction is still worse than that of the raw signal.

3.3.5 General considerations

Exact predictions of such a complex signal cannot be anticipated by any interpolation method and the question of interest would rather be whether the method can fill the gap with neuronal-like activity relevant to the brain state in this time window. Indeed, the method is not meant to provide an accurate prediction of the true signal, so that one can quantify the

**Fig. 6** The EEG signal with TMS artifact and the corrected signal from the PCA model method applied to 55 EEG channels: a CP3 signal at resting state, b P4 signal at resting state, c C1 signal with TMS during ED. In (c), the raw and corrected FP2 signal at resting state is shown where the PCA model method is applied to the 18 channels having low artifact amplitude

**Fig. 7** The EEG signal with TMS artifact from a figure-of-8 coil and the corrected signal from the PCA model method applied to 55 EEG channels: a P4 signal at resting state, b C1 signal with TMS during ED
prediction error. However, a measure of prediction error can still indicate whether the shape of the signal (amplitude, period) is well preserved. We compute the root mean square error (RMSE), i.e., the square root of the mean of the squares of the differences between predicted and true signal values in the window of correction for every channel and epoch. The RMSE is not always an indicative measure of the preservation of the neuronal-like activity in the corrected signal, e.g., the correction may be the same to the original signal but with a time lag and then RMSE is large (see Fig. 8d). To this respect, the normalized RMSE (NRMSE), defined by dividing RMSE with the SD of the true signal, can be a better indicator as it quantifies the deviation from the mean prediction (for the mean prediction NRMSE = 1). Thus, if the shape of neuronal activity is preserved, we expect to have NRMSE close or only slightly higher than one and if other characteristics of larger amplitude appear in the corrected signal, such as peaks, NRMSE would be much larger than one. The average

![Fig. 8 Three examples of TMS artifact correction with gap filling demonstrating different types of approximation of the true EEG signal. Each panel shows the true EEG signal, the EEG signal with the superposition of the TMS artifact, and the corrected signal, as shown in the legend in (a, c, e): a EEG signal F5, c EEG signal T3, and e EEG signal C4. In (b, d, f), the true and corrected EEG signals are shown as in (a, c, e), respectively, but after low pass filtering at 100 Hz.](image-url)
RMSE and NRMSE for every channel and epoch for the three states and for raw and filtered signal are shown in Table 1. The filtering gives significant improvement of RMSE in resting EEG due to the reduction of noise. There is no significant improvement in onset ED and mid-ED signals, since the same level of noise is small compared to the signal amplitude. The correction for the resting EEG is far better than for mid-ED and this is apparently due to the smaller amplitude of the signal in resting EEG. For the same reason, the correction for the onset ED EEG is better than for the mid-ED EEG (the first part of onset ED EEG has much smaller amplitude than for the mid-ED EEG). The NRMSE values are close to one for the resting EEG and onset ED EEG indicating that the corrected signal has similar fluctuations to the original one. However, for the mid-ED EEG, the often-observed peaks in the corrected signal that do not exist in the true EEG signal result in much larger NRMSE. There is a slight increase of NRMSE with filtering for all three signal types because the corrected signals tend to be smoother and thus closer to the mean prediction.

For this method, we explore two free parameters, the length \( w \) of the time window before and after the gap and the embedding dimension \( m \). Regarding \( m \), the reason for initially selecting \( m = 50 \) is to have long enough information from the past in the regressor vectors for the prediction in longer horizon to be more accurate. Moreover, a large \( m \) allows for better representation and estimation of longer duration signals, such as the epileptic seizure cycle of about \( \frac{1}{4} \) s. However, the span to the past determined by \( m \) depends on the length of the time series the training data are formed from, here defined by \( w \). As the RMSE and NRMSE for both filtered and non-filtered mid-ED EEG signals show in Table 2, for the relatively small \( w = 460 \) used in the original study in [23] and here as well, the choice \( m = 25 \) gives fluctuating signals for the gap closer to the true EEG signal. On the other hand, increasing \( m \)

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**Table 1** Average RMSE and NRMSE for the gap filling correction of EEG signals of the three different types, with and without a filter after correction

|                     | Resting EEG | Onset ED | Mid-ED |
|---------------------|-------------|----------|--------|
| RMSE (\( \mu \)V)—no filter | 13.95       | 20.23    | 44.29  |
| NRMSE—no filter    | 1.353       | 1.140    | 2.651  |
| RMSE (\( \mu \)V)—lowpass at 100 Hz | 11.00  | 19.73    | 43.86  |
| NRMSE—lowpass at 100 Hz | 1.479      | 1.192    | 2.711  |

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Fig. 9 Two examples of TMS artifact correction with gap filling when TMS is administrated during an ED in (a) and (b) and one example when TMS is administered at rest and induces ED in (c). In (a–c), the EEG signal is from F5. In (d), the signal at resting state shown in Fig. 8a is first low-pass filtered at 100 Hz, resulting in longer duration of the artifact, and then corrected.
Avoiding the disadvantages (e.g., sensitivity to initial order polynomials (e.g., reduced interpolation error), while so that it retains the advantages of interpolating with higher in Fig. 10, a shape-preserving piecewise cubic spline interpolation method. In the other examples which both introduce higher frequencies in the signal, we of the first derivative in the beginning and end of the gap, highly unrealistic with a linear component and abrupt changes the resulting gap. Since the corrected signal in this case is corrected signal would look like after linear interpolation of it is still widely used. In Fig. 10a, we show how a method on mid-ED EEG for larger \( w \) = 2400 ms. The RMSE and NRMSE for \( m = 50 \) got smaller than for the small \( w \) and for larger \( m \) (up to 300) the results do not change (see Table 2). Thus, if the stimulation setting allows the use of a larger data window before and after the TMS, e.g., single-pulse TMS or TMS blocks of lower frequency, the fluctuating signals filling the gaps can be closer to the true EEG mid-ED signals in shape. Repeating the same experiment on onset ED EEG, the fitting was somewhat worse. For the window length \( w \), we also tried other values between 460 and 2400 ms and for the same \( m \) we did not observe any improvement in the quality of the TMS artifact correction. For example, when we doubled the data window (from left and right of the TMS artifact) for the resting EEG signal, the RMSE was about the same as for the standard window length.

### 3.4 Interpolation

Even though interpolation is a simplistic approach to replace the missing signal after the artifact window has been rejected, it is still widely used. In Fig. 10a, we show how a corrected signal would look like after linear interpolation of the resulting gap. Since the corrected signal in this case is highly unrealistic with a linear component and abrupt changes of the first derivative in the beginning and end of the gap, which both introduce higher frequencies in the signal, we favor a smoother interpolation method. In the other examples in Fig. 10, a shape-preserving piecewise cubic spline interpolation has been applied. This interpolation method is designed so that it retains the advantages of interpolating with higher order polynomials (e.g., reduced interpolation error), while avoiding the disadvantages (e.g., sensitivity to initial conditions). We notice that the transitions are much smoother, particularly in the mid-ED (Fig. 10c) and onset-ED (Fig. 10d) cases.

In Table 3, we see the RMSE and NRMSE values for the aforementioned interpolation scheme and for the different signal types. We note that in terms of these metrics, interpolation performs similarly to the gap filling method for the resting and onset-ED EEG signals, and considerably better than it for the mid-ED signal. The latter happens because with interpolation, we do not have the “false” peaks observed in the gap filling method (for instance, compare Fig. 10c with Fig. 9b which comes from the same epoch).

The main advantage of these interpolation methods is that they are not very explorative, i.e., they do not diverge from the starting and ending window value by much, and thus the RMSE values stay reasonably low. However, this is not the only consideration when it comes to EEG signal correction. The interpolation methods fail substantially in producing a realistic, EEG-like signal (evident by how easy it is to spot where the correction was applied), since they cannot reproduce EEG oscillatory activity, and furthermore they alter dramatically the spectral content of the signal.

### 4 Discussion

In the present study, four methods for correction of the TMS artifact on EEG signals (i.e., FastICA, the PCA model, the gap filling method, and interpolation methods) were tested and compared on the same set of high-density EEG signals. The EEG signals were constructed by superimposing a representative TMS artifact signal on the raw EEG signal. The TMS artifact signal was extracted as the average of an ensemble of aligned EEG segments at resting state containing a single TMS pulse. The tested EEG signals had the TMS artifact at resting state, during epileptiform discharge (ED) and at the beginning of the ED (as if TMS was inducing the ED).

Both FastICA and the PCA model use a transform on the set of signals, ICA and PCA, respectively. It turned out that the TMS artifact was expressed in many components of ICA and PCA in a non-systematic manner, so that it could not be isolated by a small subset of components. Therefore, both FastICA and the PCA model methods could not correct the TMS artifact and the corrected signal still contained the artifact (in smaller amplitude) or/and the rest of the signal outside the TMS artifact window was distorted. For FastICA, many ICs were removed to reduce the TMS artifact, but these ICs contained also neuronal activity, so that either the TMS artifact was not substantially reduced or the corrected EEG signal outside the artifact deviated substantially from the true signal. The PCA model method had similar problems. Specifically, the effectiveness of the algorithm is based on the assumption that the artifact is fully recovered by the first few PCs [32],

### Table 2

Average RMSE and NRMSE with and without filtering after signal correction for varying values of the free parameters in the gap filling method, the window length \( w \), and the embedding dimension \( m \)

| Type   | Parameters | No filter | Filter at 100 Hz |
|--------|------------|-----------|-----------------|
|        | \( m \) | \( w \) | RMSE | NRMSE | RMSE | NRMSE |
| Mid-ED | 25        | 460       | 34.46 | 2.10  | 34.17 | 2.15  |
| Mid-ED | 50        | 460       | 44.29 | 2.65  | 43.86 | 2.71  |
| Mid-ED | 100       | 460       | 44.37 | 2.90  | 43.88 | 3.00  |
| Mid-ED | 50        | 2400      | 34.81 | 2.80  | 34.74 | 2.73  |
| Mid-ED | 300       | 2400      | 35.92 | 2.86  | 35.52 | 2.69  |
| Onset ED | 50        | 2400      | 41.76 | 1.49  | 41.53 | 1.53  |
which was not the case with our data. The PCA model reduced
the amplitude of the TMS artifact, while simultaneously
under-representing neuronal activity outside the artifact win-
dow, e.g., the peaks occurring during ED were smoothed out.

The third method, gap filling, is applied to each channel
independently and unlike the other two methods does not
attempt to correct the TMS artifact but rather it replaces it with
a gap and attempts to predict the signal in the gap. The pre-
diction is based on the segments on the left and right of the gap
combining a forward and backward prediction with a local
state space method. This method by construction does not
distort the signal outside the TMS artifact and does not
preserve any feature of the TMS. Indeed, for our tested EEG
signals corrupted by the TMS artifact, the gap filling method
gave satisfactory results in terms of replacing the artifactual
signal with a more realistic, EEG-like signal and the predicted
signal during the period of the TMS artifact bore some simi-
larity to the true EEG signal.

The gap filling algorithm offers a better alternative in rela-
tion to the fourth type of correction method tested, interpola-
tion, which distorts the spectral content of the signal and re-
places the gap with a signal that is not EEG-like. Unlike in-
terpolation methods, it utilizes and preserves the statistical
properties of the EEG signal itself, and fills the gap with a
signal adapted to the EEG signal before and after the gap and
having thus the morphology of the EEG signal. The interpo-
lation methods outperformed the gap filling method in terms
of RMSE in the mid-ED signal, but this is because the gap
filling method is not expected to predict well the epileptic
cycles using a correction window as small as the one we used
here.

The results on the tested EEG signals should be treated
with caution. By simply superimposing the TMS artifact to
the EEG signals, the possible causal relationship between the
artifact and the induced neuronal activity is not preserved.
However, excluding this property makes the data setting simpler. If a method is not capable of isolating the TMS artifact under these favorable conditions, then it will be unable to isolate the TMS artifact when trying to correct actual data, that is, when a causal coupling between the TMS artifact and neuronal activity does exist. For FastICA that assumes statistical independence between artifact and neuronal activity, our setting should be particularly favorable, but still FastICA did not succeed to correct the TMS artifact.

Also, the fact that the gap filling algorithm performs well here is not an indication that it will also perform well when there is a strong causal relationship between artifact and induced neuronal activity. The hypothesis when using this algorithm is that there is no excess information in the window of the TMS artifact to be corrected, so this part of the signal can simply be replaced by the predicted signal using information from the rest of the signal. So, if the neuronal activity after the period of the TMS artifact is changed as a result of the causal effect of TMS, stationarity for the whole signal (including the part replaced with a gap) is not established and the method may fail.

Estimating the efficiency of an artifact correction algorithm is a process complicated by the issue of finding the ground truth. If the ground truth of neuronal activity is not known, the output of the method cannot be evaluated. The EEG signals employed in this work, containing a superimposed TMS artifact to EEG signals at different states, represent an attempt to address this issue. An alternative approach would be to reside in qualitative measures, using time-frequency diagrams [18].

The gap filling algorithm cannot promise to find the discarded signal, but its rationale is to replace the gap with a signal with statistics similar to that of EEG. Whereas ICA, PCA, and the interpolation methods tested tend to eliminate oscillations, the gap filling algorithm preserves them, without necessarily preserving their phase. If, however, we were to receive the Fourier transform of the corrected signal, it would closely resemble an EEG signal without the TMS artifact. So, one approach for developing a gap filling correction algorithm would be to minimize the distortion of the spectral content of the EEG signal, which is a topic for further research.

5 Conclusion

We conclude that out-of-the-box approaches (FastICA, PCA model, interpolation) fall short in correcting TMS-EEG artifacts under adverse experimental conditions. Specifically, they were insufficient to tackle the size of the artifact compared to the EEG recording in the restrictive settings of the block design of the experiment, or they produced non-EEG-like signals. A more targeted approach was tested on the same settings to assess whether it would overcome the insufficiency of general-purpose approaches. Indeed, the so-called gap filling method yielded satisfying results for the pilot data. Even though it performed well on a type of non-stationary pilot data, it is expected not to perform as well for real data due to their diverse non-stationary nature. Similarly to the other methods used in the study, it cannot be expected to reliably uncover evoked neuronal activity masked by the artifact. However, the gap filling method can still be used to replace the contaminated by the artifact EEG signal with a more realistic, in terms of spectral properties, EEG surrogate signal.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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