Reduction of TMS Induced Artifacts in EEG Using Principal Component Analysis

Esther M. ter Braack, Benjamin de Jonge, and Michel J. A. M. van Putten, *Member, IEEE*

***Abstract*—Co-registration of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) is a new, promising method for assessing cortical excitability and connectivity. Using this technique, a TMS evoked potential (TEP) can be induced and registered with the EEG. However, the TEP contains an early, short lasting artifact due to the magnetic pulse, and a second artifact, which depends on the location of stimulation and can last up to 40 ms. Different causes for this second artifact have been suggested in literature. In this study, we used principal component analysis (PCA) to suppress both the first and second artifact in TMS-EEG data. Single pulse TMS was applied at the motor and visual cortex in 18 healthy subjects. PCA using singular value decomposition was applied on single trials to suppress the artifactual components. A large artifact suppression was realized after the removal of the first five PCA components, thereby revealing early TEP peaks, with only a small suppression of later TEP components. The spatial distribution of the second artifact suggests that it is caused by electrode movement due to activation of the temporal musculature. In conclusion, we showed that PCA can be used to reduce TMS-induced artifacts in EEG, thereby revealing components of the TMS evoked potential.**

***Index Terms*—Artifact reduction, electroencephalography, principal component analysis (PCA), transcranial magnetic stimulation.**

I. Introduction

CO-REGISTRATION of transcranial magnetic stimulation (TMS) [1] and electroencephalography (EEG) is a relatively new and promising method for assessing cortical excitability and connectivity. TMS-EEG provides researchers with the opportunity to stimulate the brain and directly measure the response of the stimulated area, without the need of detecting a peripheral response. When TMS is applied while recording EEG, a characteristic waveform—the TMS evoked potential (TEP)—is induced in the EEG. The methodology of measuring and analyzing the TEP is similar to other event-related potential measurements, such as the visual or auditory evoked potential. Assuming that the stimulus always induces a specific response in the EEG, and considering all other brain activity as uncorrelated, the response can be extracted by averaging over several stimuli.

The TEP shows characteristic components at different latencies, and is most well defined on electrode position Cz. Negative components at 15, 45, and 100 ms and positive components at 30, 60, and 180 ms have been reported in several studies [2]–[9]. Some authors describe even earlier peaks: a negative component at 7–10 ms and a positive component at 13–14 ms [2], [5].

To perform TMS-EEG measurements, special equipment is required, in particular to avoid saturation of the amplifier due to the strong electromagnetic pulse [6]. The two most common used techniques are using a sample-and-hold circuit that short-circuits the amplifier input to ground for about 5 ms during the TMS pulse [10], or using an amplifier in which the sensitivity and operational range can be adapted [2], [11], also referred to as a slew rate amplifier [12], [13]. Adapting these properties ensures that the amplifier does not saturate due to the TMS pulse. In the present study, we use a third technique: a dc amplifier, which has no capacitive elements and therefore does not saturate after a TMS pulse. The TMS pulse artifact measured by this amplifier is in the order of millivolts and lasts only approximately 5 ms. Because of the short duration of this artifact, the early part of the TEP can be analyzed, as there is no interference with these early responses. In various cases, however, a second large amplitude artifact which slowly recovers is observed as well. This second artifact, starting from the time of the TMS pulse with a large positive peak at 5 ms, a large negative peak at 10 ms and lasting up to tens of milliseconds [14], may obscure the early components of the TEP. As these early components reflect the excitability of the stimulated area, they have potential value as biomarkers for changes in cortical excitability, as may be present in epilepsy or stroke. Therefore, successful prevention of occurrence or removal of this second artifact is desirable.

Different causes for this second artifact have been suggested in literature. Because of its spatial distribution over the scalp and as the artifact occurs more frequently when temporal regions of the head are stimulated, a possible origin is the activation of the cranial muscles [14]–[16]. Alternatively, the artifact may be caused by the capacitive properties of the electrode–gel–skin circuits [17]. A third possibility is the direct in-

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E. M. ter Braack is with the Department of Clinical Neurophysiology, MIRA Institute for Technical Medicine and Biomedical Technology, University of Twente, 7500 KA Enschede, The Netherlands (e-mail: e.m.ter-braack@utwente.nl).

B. de Jonge was with the Department of Biomedical Engineering, MIRA Institute for Technical Medicine and Biomedical Technology, University of Twente, 7500 KA Enschede, The Netherlands. He is now with TMSi, 7575 EJ Oldenzaal, The Netherlands (e-mail: benjamindej@gmail.com).

M. J. A. M. van Putten is with the Department of Clinical Neurophysiology, MIRA Institute for Technical Medicine and Biomedical Technology, University of Twente, 7500 KA Enschede, The Netherlands, and also with the Department of Neurology, Medisch Spectrum Twente, 7513 ER Enschede, The Netherlands (e-mail: m.j.a.m.vanputten@utwente.nl).

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duction of currents in the electrode wires [18]. Although precautions can be used to limit these contributions to the TEP artifacts, ranging from reducing the stimulus intensity and changing the tilt and rotation of the coil [14], the use of needle electrodes [17] or rearrangement of electrode wires [18], in various experimental conditions significant artifacts remain present. Although the origin is not completely clear, it is agreed that the artifact and EEG signal come from independent sources, making independent or principal component analysis (ICA or PCA) ideal techniques to suppress this artifact.

A few papers have proposed signal processing techniques to remove the artifact from TMS-EEG recordings, such as Kalman filters [19] or ICA [16], [20], [21]. However, these methods were aimed only at the first TMS artifact [19], [21], or did not discuss a possible effect on the physiological waveforms of the TEP when artifactual components were removed [20]. Only one study showed that PCA can be used successfully to remove the second artifact [15]. However, it was combined with a topographic projection method and applied to a limited number of subjects $(n = 3)$ [15]. In addition, the TEP that was obtained after artifact removal was very low in amplitude, because also parts of the TEP (with the same topography as the second artifact) were removed by PCA, although the amount of suppression was exactly known.

We present a method to reduce both the first and second artifact in TMS-EEG data using only PCA, evaluated in a larger number of subjects. In our approach, no assumptions are made about the topographical distribution of the artifact. Ideally, the artifact removal technique should only reduce the TMS artifact, thereby revealing early components of the TEP, without a significant effect on the later components of the TEP. Therefore, we also evaluated if PCA attenuated later parts of the response, which were not corrupted by artifacts.

II. Materials and Methods

A. Subjects

Eighteen healthy subjects (11 males, mean age 28 years, all right-handed) participated in this study after giving written informed consent. The experimental protocol was approved by the local ethical committee (Medisch Spectrum Twente) and was in accordance with the declaration of Helsinki.

B. Stimulation

Single biphasic TMS pulses, with pulse duration of 400 μs and inter-pulse interval of 4 s, were delivered manually using a 70 mm figure-of-eight air film coil and a Magstim Rapid^2 stimulator. The coil was placed tangentially with the handle pointing backward and laterally at an angle 45° away from the midline over four targets: the hot-spot of the abductor digiti minimi muscle (ADM) in the right and left motor cortex; and Brodmann area 19 in the right and left hemisphere. The maximum stimulator output was 1.5 T; stimulation intensity for the targets in the left hemisphere was set at 110% of the resting motor threshold (RMT) of the left ADM hot spot and at 110% RMT of the right ADM hot spot for the targets in the right hemisphere. The motor threshold was defined as the lowest stimulus intensity that produced at least five MEPs of at least 50 μV out of 10 consecutive stimuli [22]. There were five sessions for every subject; in each session we applied 75 pulses at all four targets.

C. TMS Targeting

Positioning of the coil was achieved using a robot-navigated system (Advanced Neuro Technology, Enschede, The Netherlands). A headband carrying four passive reflective markers was fixed to the head of the subject and tracked by a Polaris infrared camera system (Northern Digital, Waterloo, ON, Canada). The robot and the tracking system were registered to a common coordinate system using a calibration procedure. The robot-guided TMS coil was added to the coordinate system by registration of three reference positions on the coil using a tracking pointer. In all subjects, a 1.5 T MRI scan of the head was available. The MRI scan was used to create a subject-specific head model; this model was then registered to the subject's head and the coordinate system by collecting three landmarks and ∼300 additional points on the scalp with a tracking pointer.

D. EEG and EMG Recording During TMS

The EEG was recorded continuously during TMS using a dc amplifier and a TMS-compatible 64-electrode cap (ANT, Enschede, The Netherlands). Impedances were kept below 5 kΩ. The ground electrode was placed between electrode positions Fz and Fpz. We used a common average reference for the recordings. To determine the RMT, we recorded the EMG using an additional amplifier (TMSi, Oldenzaal, The Netherlands) connected to the EEG amplifier, ensuring synchronized measurements. Surface electrodes were placed in a belly–tendon montage over the ADM muscle. The ground electrode was placed on the dorsal side of the wrist. EEG and EMG data were low-pass filtered with an anti-aliasing filter with a cutoff frequency of 550 Hz and sampled at 2048 Hz.

E. EEG Analysis

We assumed that no differences in artifact were present when recording during different sessions, therefore all 375 applied pulses per target per subject were used for analysis. The recorded EEG data were divided in trials of 4 s (2 s before and after a TMS pulse). We used the common average reference for analyzing the data. Trials with eye blinks were automatically detected and these were rejected for further analysis. PCA using singular value decomposition was used to decompose the data into different components.

F. Principal Component Analysis

PCA [23] is a well-established multivariate data technique which finds the direction in the data with most variation. It is expected that the direction with most variation contains the TMS induced artifacts, because of the large amplitude difference between artifact and EEG signals.

Initially, we subtracted the mean from dataset $\mathbf{X}$, which contains the EEG data, the rows being the number of electrodes, and the columns being the number of data points. The covariance matrix $\mathbf{C}$ was then calculated, given by

$$C = \frac{1}{n} X X^T \tag{1}$$

in which n is the number of channels, and T means transposed. From the covariance matrix $\mathbf{C}$ the eigenvectors and eigenvalues are calculated and sorted according to their eigenvalue. Singular value decomposition is now used to decompose dataset $\mathbf{X}$ in matrices $\mathbf{U}$, $\mathbf{S}$, and $\mathbf{V}$

$$X = USV^T. \tag{2}$$

Orthogonal matrix $\mathbf{U}$ captures the eigenvectors calculated in the previous step in each column; $\mathbf{S}$ contains the singular values (square root of eigenvalues of $\mathbf{X}\mathbf{X}^{\mathrm{T}}$) and orthogonal matrix $\mathbf{V}$ contains the eigenvectors of $\mathbf{X}^{\mathbf{T}}\mathbf{X}$.

Matrix $\mathbf{S}$ is ordered from high to low values. The highest value describes the component captured in the eigenvector with the highest variation. We performed PCA using 40 calculated components on each individual trial. Using the eigenvector matrix $\mathbf{U}$ and singular values in $\mathbf{S}$, the number of components to be removed can be selected.

The data can then be reconstructed with only the remaining principal components ($\tilde{\mathbf{U}}$), which are ideally the components that do not describe the artifact

$$X_{\mathrm{corrected}} = \tilde{U} * \tilde{U} * X_{\mathrm{original}}. \tag{3}$$

For all subjects, the first 20 principal components were removed, one component at a time. After removing each consecutive component, the TEP was obtained by averaging over trials.

G. Evaluation of Artifact Removal

For evaluation of the effect of the removal of the PCA components on the amplitude of the artifact and TEP, we visually detected the artifact and TEP components for every consecutive PCA component that was removed. We chose two electrodes to evaluate the artifact removal, one directly at the site of TMS (which was C3 for left motor cortex stimulation and C4 for right motor cortex stimulation) and one in an area where the TEP is the most well defined (Cz). The first large—positive or negative—peak between 0 and 5 ms after TMS administration represents the first artifact. The large positive peak between 5 and 10 ms was used as a quantitative measure for the second artifact. Changes in the absolute values of both artifacts for the electrode of stimulation, C3 or C4, using the unfiltered signal, were used as performance measures. In addition, we also analyzed the first artifact at electrode Cz. We then applied a low-pass Butterworth filter with a cut-off frequency of 150 Hz and visually analyzed the TEP at electrode Cz. The P30, N45, P60, and N100 components of the TEP were visually assessed, both for left and right motor cortex stimulation. We subsequently calculated the peak-to-peak amplitudes P30-N45 (referred to as P30), P60-N45 (referred to as P60), and P60-N100 (referred to as N100). All initial amplitudes (artifact and TEP components) were normalized to 1. The amplitude changes were subsequently evaluated as a function of the number of removed principal components.

III. Results

A first, large artifact, with a duration of approximately 5 ms, was seen when stimulating the motor cortex and Brodmann area 19. In 16 out of 18 subjects, an additional artifact was visible after stimulation of the motor cortex, which was not present when Brodmann area 19 was stimulated. This second artifact was located temporal from the stimulated target. The topography and average power of the first and second artifact are illustrated in Fig. 1, showing a grand average of these 16 subjects.

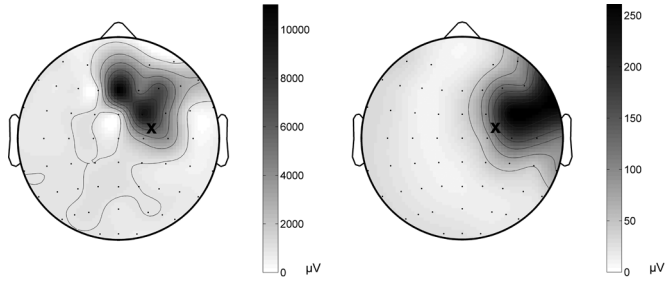

Fig. 1. Topoplots of signal power for the first (left) and second (right) artefact, after stimulation at the right motor cortex. Note the large difference in amplitude between the first and second artefact. When Brodmann area 19 was stimulated, no second artefact was observed. Grand average of 16 subjects. X denotes the stimulus position.

In Fig. 2, responses in channels C4 and Cz from two subjects are shown before and after PCA correction. In one of these subjects a large second artifact was seen: the first artifact ends at approximately 5 ms; the second artifact shows a positive peak at 8 ms and a negative peak at 10 ms, after which it slowly recovers. Since the TMS coil was positioned just above electrode C4, this is one of the channels that shows the largest second artifact. The TEP, however, is most well defined at electrode Cz. TEP components at 30, 45, 60, and 100 ms are visible at this electrode in the uncorrected response. For the two subjects without a second artifact, earlier components at Cz can be identified in the uncorrected signal, but for subjects with a large second artifact, these only become visible after removing three to four principal components. These early peaks are similar in latency for all subjects (N10—P15—N20 for Cz) and correspond to early TEP components reported in literature [2], [5]. At electrode C4, different early TEP components become visible as well (N10—P15—N18). After removal of five principal components, the amplitude of both first and second artifact is greatly reduced, although there is some residual left. After rejection of more PCA components, the TEP components at 30, 45, and 60 ms also reduce in amplitude. Latencies of these peaks do not change after PCA correction.

In Fig. 3, the TEP at all electrodes is shown for a single subject after stimulation of the left motor cortex. The effects of removing the first 10 principal components on the TEP for the same subject is shown in Fig. 4. The artifacts are greatly reduced, although there is still some residual artifact in the frontotemporal electrodes visible. These remaining artifacts disappear when more components are removed, but then the TEP also reduces in amplitude; this trade-off is shown in Fig. 5.

The effect of removing 1–20 principal components from the data obtained in 16 subjects after stimulating the right motor cortex is shown in Fig. 5. The reduction in amplitude of the first artifact is the largest after removal of the first component, resulting in a reduction of amplitude to about 0.25 of the initial value for electrode Cz and C4. However, because the original amplitude is very high, the remaining artifact is still significantly

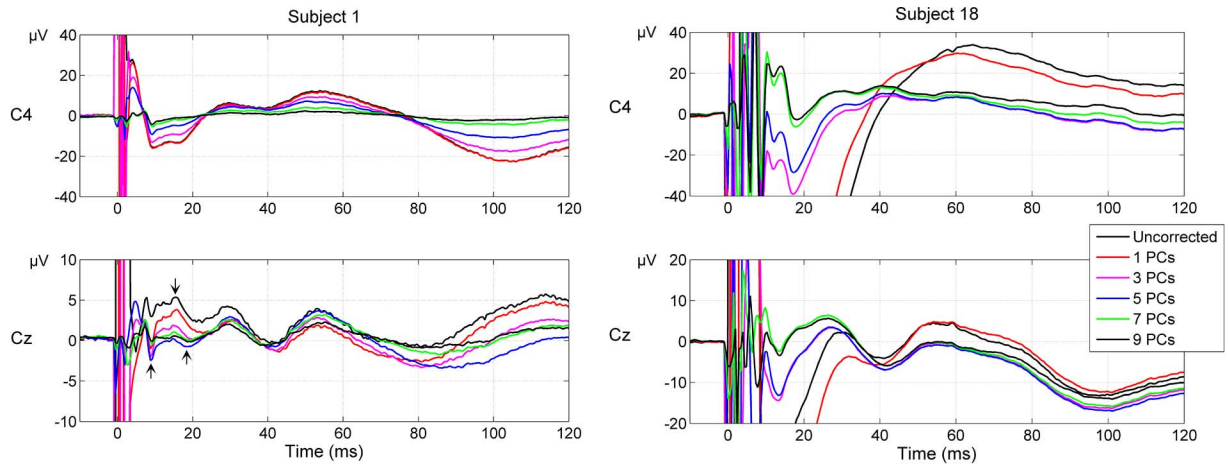

Fig. 2. PCA performance is shown for the unfiltered recordings at electrode C4 (top) and Cz (bottom) in two subjects. Note the different scaling at the y-axes. Subject 1 (left) did not show a second artefact, while subject 18 (right) had a large second artefact. TEP components at 30, 45, and 60 ms are clearly visible at Cz in the uncorrected response in both subjects; earlier components only become visible after PCA correction in subject 18, while in subject 1 these could be identified without PCA (indicated by the arrows). TMS was targeted at the right motor cortex, above electrode position C4.

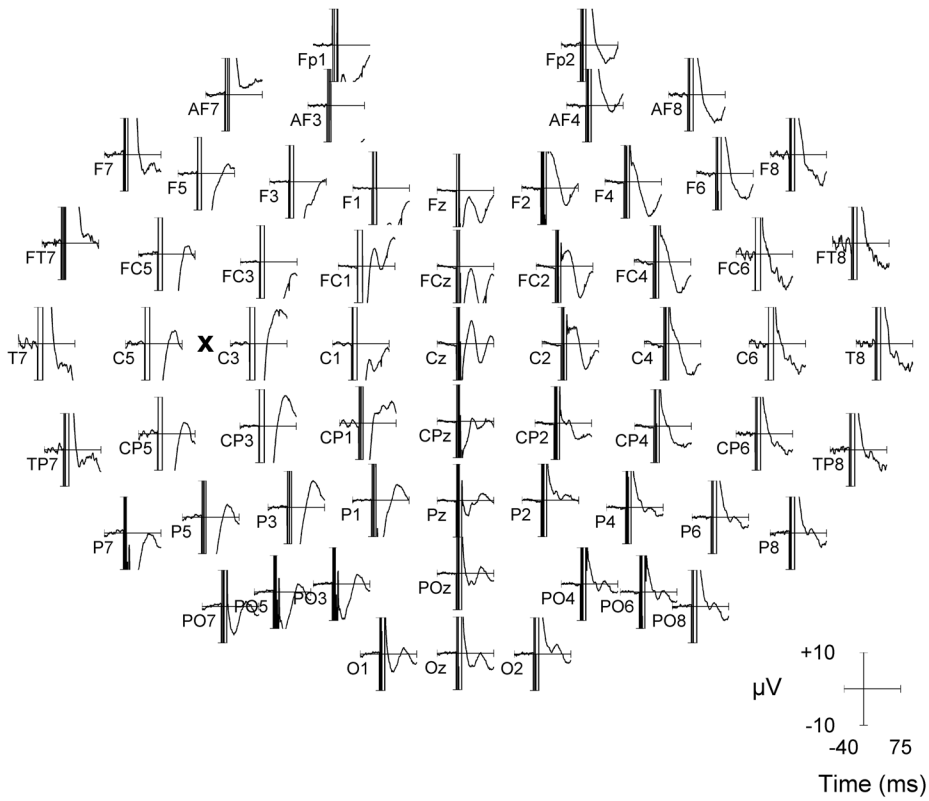

Fig. 3. TEP before artefact correction using PCA in a subject 10. The left motor cortex (around C3) was targeted with TMS.

larger than the TEP components. After removing approximately five principal components, the artifact amplitude approaches zero. Removing the second artifact proves to be more difficult: after five PCA components, the amplitude is below 40% of the initial value. For the TEP components, there is a large variation between subjects in the amplitude change. However, on average the amplitude of the P60 and N100 stays within a 20% decrease if the first five components are removed. Because the second artifact lasts up to 30–40 ms, the presence of the P30 becomes more pronounced after PCA components are removed, leading in some subjects to an increasing P30 amplitude. The large variation in P30 amplitude between subjects is a result of the differences in the amount of second artifact that is present in each individual subject, with corresponding inter-individual differences in the amount of reduction after PCA.

IV. Discussion

TMS-EEG is a promising technique to explore cortical excitability by analysis of the different waveforms present in the TMS-evoked potential. However, in particular during the first

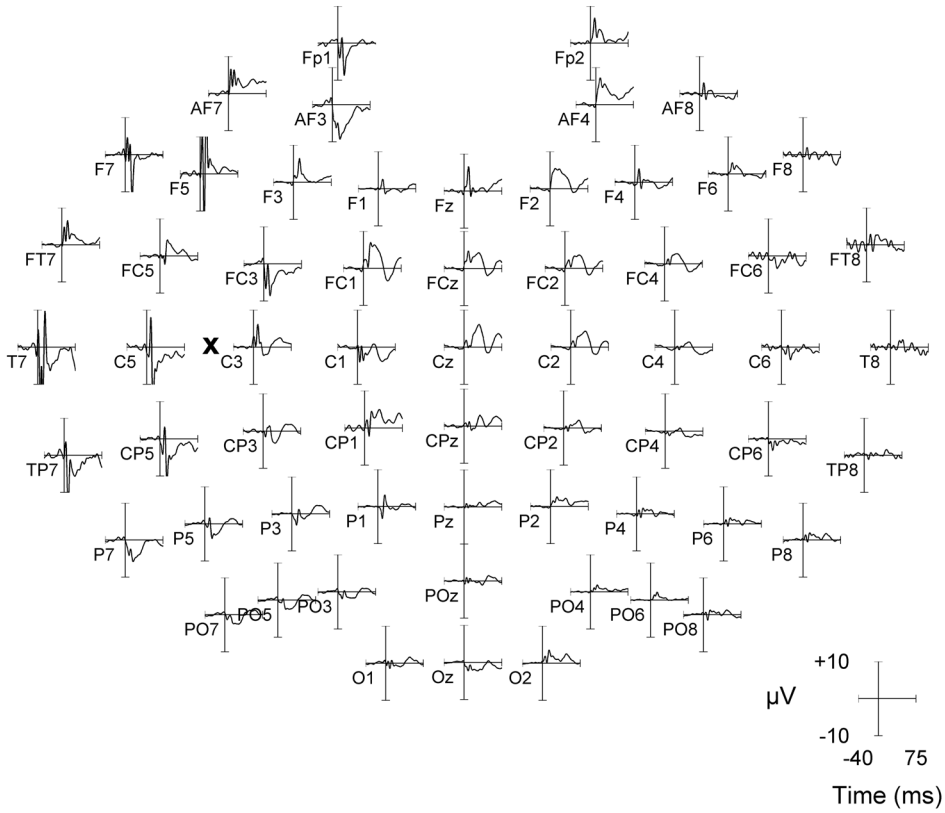

Fig. 4. TEP after removing 10 principal components in subject 10. The left motor cortex (around C3) was targeted with TMS. The artefact is greatly reduced as compared to Fig. 3, while the main components of the TEP are preserved. However, there is still some artefact remaining at the left frontotemporal electrodes.

30 ms, artifacts may be present that obscure the interpretation of early responses. Here, we explore the nature of the TMS artifacts, and if PCA is a suitable method to remove the various artifactual components.

The amplitudes of both first (0–5 ms) and second (5–10 ms) TMS artifact were strongly reduced by removing components using PCA. With approximately five components removed, the later responses of the TEP (P60 and N100) stayed within a 20% decrease. With five removed components, the reduction in artifact amplitude is sufficiently large to allow further signal processing, such as filtering and analysis of the various latencies of the TEP waveforms. In all subjects, this cutoff number of approximately five components was found.

The number of components to be removed has to be considered carefully for each individual subject: with too few components the artifact is not reduced enough to see the early TEP peaks, and with too many components the later components of the TEP become very small. In addition, the electrode of interest is also important. For the area directly surrounding the TMS targeting, more principal components have to be removed to obtain a sufficient artifact reduction, while for electrodes further away from the TMS target the same result is obtained with only a few removed components. Although the second artifact is reduced less than the first artifact, the artifact suppression by removing five principal components is strong enough to reveal early TEP components, which was the aim of this study. Computation time was 5–6 min for one target in a single subject.

The spatial distribution of the evoked potentials showed that when the motor cortex was stimulated, the first artifact is located more frontal to the target, while the second artifact can be found at the temporal areas. When the occipital region at Brodmann area 19 was stimulated, the first artifact was situated just beneath the target, and no second artifact was observed. These findings make a muscular origin for the second artifact plausible. However, the duration of the artifact is too long for a compound muscle action potential, which lasts only a few milliseconds. A possible explanation is that the artifact is not the muscle activation itself, but a subsequent movement of the electrodes that are located above the muscle, induced by the muscle contraction. This would also explain why some authors achieved better results with needle electrodes [17], because then the amount of electrode movement is presumably limited.

Another possible cause for the second artifact is an induction effect in the wires of the EEG cap [18]; the specific distribution of the artifact may be caused by a different position of the wires at the temporal sides of our EEG cap. Indeed, in our subjects we do not observe the second artifact when stimulating the top of the head or the occipital regions. In measurements using a phantom with a TMS-compatible EEG cap, stimulating at different locations, a second artifact was never observed, providing further evidence that wiring is not responsible for the second artifact. A similar technique was already used in literature to investigate the first TMS artifact [11], and Mutanen *et al.* also showed that the second artifact was not present using a phantom

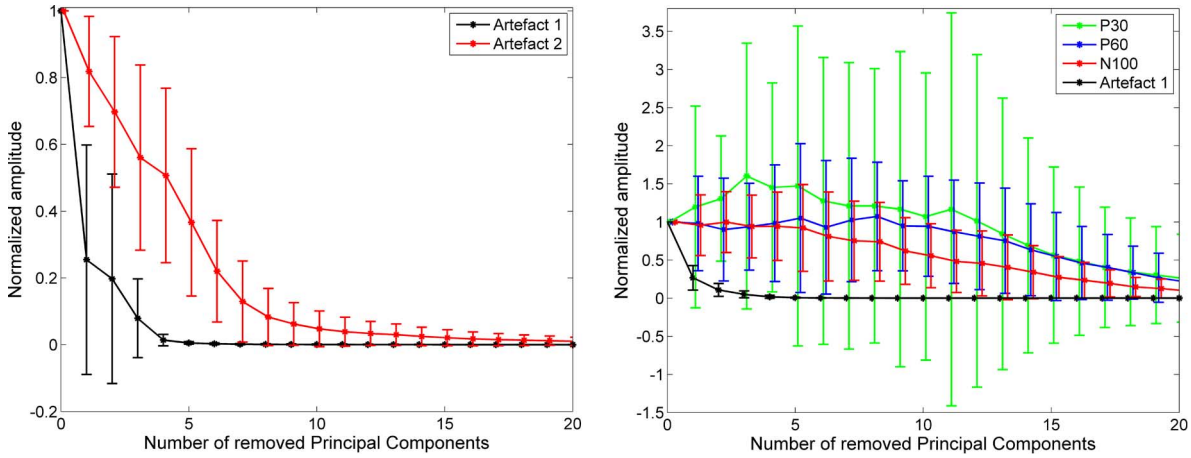

Fig. 5. Normalized amplitude of the first and second artefact for electrode C4 (left) and of the first artefact, P30, P60, and N100 as a function of the number of removed components for electrode Cz (right). Errorbars represent the standard deviation. Grand average of 18 subjects. TMS was targeted at the right motor cortex.

head [14]. Although the contribution of a capacitive effect of the electrode–skin interface [17] cannot be excluded in our experiments, this is unlikely as well, as the second artifact was not present during stimulation over the occipital electrodes.

Recently, PCA combined with a topography-based method has been reported to be able to completely remove TMS induced artifacts, which were assumed to originate from a muscle contraction [15]. These authors determined the components to be taken out based on the topography of this muscle activity, acknowledging the fact that also brain activity with the same topography is strongly suppressed. This implies that brain activity generated by sources just underneath the coil—most likely the areas activated first by the pulse, and therefore the areas responsible for the earliest components of the TEP—will be reduced, although the amount of attenuation is known. This is especially important when the area activated by TMS is located at the site where the artifact is most visible, for example at temporal regions. The TEP components were found to be significant in the calculated global mean field potential (GMFA) after artifact reduction, but the presence of early TEP components before and after artifact reduction was not shown.

In our implementation, no assumptions about topography are made, resulting in an evenly reduction of the artifact (and TEP when too many components are removed) over the cortex. Furthermore, in the approach described in [15], the PCA components were calculated after initial averaging of the TEP, while we apply PCA on single trials. At present, it is not clear which method is most suitable. An additional improvement in topography-based PCA may be achieved when less principal components are removed.

After applying PCA, removing approximately five principal components results in an artifact suppression of more than 10 times. Early components of the TEP, which were initially obscured by the second artifact, are revealed using this technique. There were only minor effects on the later components of the TEP, except for the P30 which showed large variations in amplitude, probably because this TEP component is largely affected by the second artifact. Although both artifacts are strongly reduced by PCA, complete removal cannot be guaranteed with our approach. The low-amplitude peaks that remain, may still be small remainders of the artifacts, this may indeed be true for the negative peak around 10 ms in Cz, which is at the same latency as the large negative peak in the second artifact [14]. On the other hand, it is likely that reducing the amplitude of both artifacts did reveal true brain responses that were initially hidden, especially because latencies of these emerging early peaks—also the N10—were similar to early TEP components reported in literature [2], [5]. In these two studies, no second artifact was observed in the data, and no artifact rejection technique was used that could have induced small fluctuations resembling TEP components. In any case, small effects on the response itself have to be taken into account as well when analyzing the data further, especially when applying source analysis.

In conclusion, the TEP response obtained in TMS-EEG measurements contains an early artifact due to the magnetic pulse, and a second artifact. The second artifact depends on the location of stimulation, and is most likely caused by muscle activation due to the TMS pulse, possibly followed by electrode movements. We showed that PCA can be used to reduce TMS artifacts so that interpretation of early responses is possible, without the need for additional or complex signal analysis methods. This is particularly relevant when the TMS is targeted at the temporal regions of the brain, for example in research concerning auditory or speech functions, or when the seizure onset zone is stimulated in patients with temporal lobe epilepsy.

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Esther M. ter Braack studied technical medicine at the University of Twente, Enschede, The Netherlands. In 2009, she started as a Ph.D. student in the Department of Clinical Neurophysiology, MIRA-Institute for Biomedical Engineering and Technical Medicine, University of Twente, Enschede, The Netherlands. Her Ph.D. project focuses on combining TMS and EEG in epilepsy research.

Benjamin de Jonge received the M.Sc. degree in biomedical engineering from the University of Twente, Enschede, The Netherlands, in 2011.

His interests include bio-electric signals and signal processing with a main focus on the application of signal processing in the clinical practice. He is now a Product Specialist at TMSi, Oldenzaal.

Michel J. A. M. van Putten (M'12) studied medicine at Leiden University, Leiden, The Netherlands, and applied physics at Delft University of Technology, Delft, The Netherlands. In 2000 he became a board certified neurologist and received the Ph.D. degree from Delft University of Technology.

He is a Professor of Clinical Neurophysiology at the MIRA-Institute for Biomedical Engineering and Technical Medicine, University of Twente, Enschede, The Netherlands. His main research interests include neuromonitoring, epilepsy, and ischemia.