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## Tensor decomposition of TMS-induced EEG oscillations reveals data-driven profiles of antiepileptic drug effects

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1 *Highlights*

- 2 • TMS-EEG allows probing of human brain excitability and functionality in health and  
3 disease.
- 4 • Tensor decomposition to identify key features of high-dimensional EEG data.
- 5 • Using this data-driven approach, we reveal the effects of antiepileptic drugs on TMS-  
6 EEG.

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1 **Abstract**

2 **Background:** Transcranial magnetic stimulation combined with electroencephalography  
3 (TMS-EEG) is a powerful tool to probe human cortical excitability. The EEG response to TMS  
4 stimulation is altered by drugs active in the brain, with characteristic “fingerprints” obtained  
5 for drugs of known mechanisms of action. However, the extraction of specific features related  
6 to drug effects is not always straightforward as the complex TMS-EEG induced response  
7 profile is multi-dimensional, indexed over space, time, frequency, subjects and drug  
8 conditions. Analytical approaches can rely on *a-priori* assumptions within each dimension or  
9 on the implementation of cluster-based permutations which do not require preselection of  
10 specific limits but may be problematic when several experimental conditions are tested.

11 **Methods:** We here propose an alternative data-driven approach based on PARAFAC tensor  
12 decomposition, which provides a parsimonious description of the main profiles underlying  
13 the multidimensional data. We validated reliability of PARAFAC on TMS-induced oscillations  
14 before extracting the features of two common anti-epileptic drugs (levetiracetam and  
15 lamotrigine) in an integrated manner.

16 **Results:** PARAFAC revealed an effect of both drugs, significantly suppressing oscillations in  
17 the alpha range in the occipital region. Further, this effect was stronger under the intake of  
18 levetiracetam.

19 **Conclusions:** This study demonstrates, for the first time, that PARAFAC can easily disentangle  
20 the effects of subject, drug condition, frequency, time and space in TMS-induced oscillations.

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## 1 **1. Introduction**

2 Transcranial magnetic stimulation (TMS) is a non-invasive tool to probe neurophysiological  
3 processes in the human brain. A TMS pulse depolarizes the stimulated neuronal population  
4 and remote anatomically connected regions <sup>1</sup>. The registration of TMS effects with  
5 electroencephalography (EEG) allows to quantify and characterize spread of neural activation  
6 that follows in time, spatial and frequency domains <sup>2</sup>. The summation of synaptic potentials  
7 produces a series of time-locked positive and negative deflections visible in the EEG signal,  
8 termed the TMS-evoked potentials (TEPs). TEPs are a sequence of peaks which reflect cortical  
9 reactivity and changes in their amplitude and latency reflect changes in cortical activity <sup>3</sup>. In  
10 addition, brain responses to TMS can be interrogated applying a time-frequency analysis at  
11 single trial level removing the evoked (i.e. TEPs) component from the signal. TMS-induced  
12 oscillations are the result of this analytical approach and they provide non-phase locked  
13 neural information <sup>4</sup>.

14 TEPs and TMS-induced oscillations are outcome measures used to characterise brain states  
15 in health, diseases and under experimental conditions such as drug manipulation <sup>5</sup>. Previous  
16 work showed that TMS-EEG is a powerful tool to investigate effects of drugs acting in the  
17 human brain <sup>6-10</sup>. In these studies, the effects of drugs were quantified in term of differences  
18 between conditions (or subjects) in evoked activity in specific time windows corresponding  
19 to TEPs and in specific sets of EEG electrodes. A cluster based permutation approach is the  
20 golden standard used to overcome the problem of multiple comparisons. It requires an a-  
21 priori selection of time windows or a post-hoc correction for the large number of non-  
22 independent comparisons across many tested conditions. It seems highly likely that  
23 important effects will be lost through inadvertent selection of the “wrong” time windows  
24 and/or electrodes, or through the necessarily harsh post-hoc correction for multiple non-  
25 independent comparisons.

26 The high dimensionality of TMS-EEG data is a challenge for analysis and interpretation, and  
27 motivates approaches to simplify the data by reducing the dimensionality. Specifically, we can  
28 hypothesise that TMS stimulation of the brain gives rise to activity in specific brain networks  
29 following stimulation, and that these networks will have a specific spatial distribution and  
30 specific spectral characteristics (i.e. the network operates in a particular frequency range) –

1 but identifying such underlying patterns in highly multidimensional data is difficult. Here, we  
2 apply a methodology based on tensor decomposition to reveal such underlying patterns.

3 The term “tensor” refers to a multi-way (i.e. multidimensional) array, that is a collection of  
4 variables that can be indexed by more than two terms. Whereas the position of an element  
5 in a vector or matrix is determined, respectively, by one (e.g.,  $i$ ) or two indices (e.g.,  $i,j$ ), the  
6 values in a tensor are indexed by more than two parameters:  $i, j, k$  <sup>11</sup>. In a similar way to how  
7 matrix decompositions (e.g., principal component analysis) can represent a two-dimensional  
8 array (a matrix) as a product of factor matrices, tensor decompositions allow us to extract  
9 from seemingly complex multidimensional data parsimonious and unique representations of  
10 underlying patterns <sup>11,12</sup>. Since the introduction of the PARAFAC algorithm, which  
11 decomposes a tensor into a sum of outer products of low-rank components <sup>13</sup>, tensor  
12 decompositions, and PARAFAC in particular, have been used in a wide range of studies of EEG  
13 activity <sup>14</sup>. Seminal studies focused on the analysis of event-related potentials <sup>15,16</sup>.  
14 Subsequent tensor decompositions of EEG data enabled the inspection of time-frequency  
15 representations of EEGs during cognitive states <sup>17</sup>. Tensor decomposition has also been used  
16 in artefact rejection and estimation of seizure onset zone <sup>18,19</sup>. Other applications include  
17 localisation of EEG sources <sup>20</sup>, connectivity estimation <sup>21</sup>, brain computer interfaces <sup>22,23</sup>, and  
18 feature extraction in clinical and psychological studies <sup>24-26</sup>. Tensor decomposition are also  
19 useful when fusing EEG with other datasets <sup>27-29</sup>. Overall, the use of tensor decompositions is  
20 advantageous over matrix factorisations when the data are naturally multidimensional like in  
21 the case of EEG, and TMS-EEG <sup>12</sup>.

22 In this study, we sought to apply a data-driven approach, exploiting the multidimensional  
23 structure of previously collected TMS-EEG data, allowing a parsimonious dimensionality  
24 reduction that summarises effects in the high-dimensional data. We hypothesise that  
25 PARAFAC will be able to reveal underlying patterns of activity with different topographical  
26 (accounting for the spatial distribution of a brain network), temporal (indicating time period  
27 after TMS stimulation during which the network is active) and spectral (informing about the  
28 typical operating frequency of the network) profiles that will be characteristic of the effects  
29 of each type of anti-epileptic drug (AED) in the TMS-EEG data without a-priori assumptions.

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## 1 **2. Methods**

### 2 *2.1 Subjects*

3 Thirteen healthy male volunteers aged 19-34 years (mean age 25.2 years, SD =  $\pm$  4.62)  
4 participated in the study after written informed consent was given. All subjects were classified  
5 as right-handed according to the Edinburgh Handedness Inventory<sup>30</sup> and underwent physical  
6 examination and screening for any contraindications to TMS or study drugs<sup>31</sup>. The College  
7 Research Ethics Committee (CREC) of King's College London approved the research, which  
8 was performed in accordance with relevant guidelines and regulations. Informed consent was  
9 obtained from all participants. The TMS-evoked EEG potential (TEP) analyses of this sample  
10 have been published previously<sup>7,32</sup>.

### 11 *2.2 Experimental design*

12 We performed a double-blind, randomized, placebo-controlled, crossover study to  
13 investigate the impact of levetiracetam (LEV, 3000 mg) and lamotrigine (LTG, 300mg) on TMS-  
14 induced EEG oscillations. Each subject participated in three experimental sessions in total,  
15 administered lamotrigine, levetiracetam or placebo in each session in a randomized order,  
16 spaced at least one week apart to allow a washout period. At each session, we first performed  
17 baseline pre-drug TMS-EEG recording. Later, the post-drug recording was performed two  
18 hours after drug ingestion, please see the details of the experimental setting and protocol in  
19 the supplementary section A.1.

### 20 *2.3 Data analysis*

#### 21 *2.3.1 TMS-EEG data construction*

22 TMS-induced oscillations were analysed using MATLAB<sup>®</sup> (Mathworks Ltd, USA, R2012b) (The  
23 Mathworks Inc.) and FieldTrip toolbox<sup>33</sup>. After excluding records/trials with prominent eye  
24 movements, blinks, and muscle artefacts (on the basis of visual inspection), EEG data was  
25 analyzed using an established multistep procedure<sup>34</sup>. Data was down sampled to 1 kHz,  
26 segmented 1 s before and after the pulse, and linearly interpolated for  $\pm$ 10 ms to remove the  
27 TMS artefact. Bad channels were removed from the EEG, and the signal was reconstructed by  
28 interpolating the surrounding electrode signals. Data was then notched filtered (50 Hz).  
29 Independent Component analysis (ICA) was applied to remove TMS-related artifacts (i.e., the

1 cranial muscle response, the recharging of capacitors, and related exponential decay artifacts  
2 <sup>35-37</sup>, as well as further muscle and ocular activity. Finally, remaining data were re-referenced  
3 to the average of all electrodes, baseline corrected (from -1000 to -50 ms) and band-pass  
4 filtered (1-80 Hz).

5 After that, for each segment we estimated its time-frequency plot by applying a Hanning  
6 taper windowed fast Fourier transform (FFT) with frequency-dependent window length  
7 (width: 3.5 cycles per time window, time steps: 10 ms, frequency steps: 1 Hz from 4 to 45 Hz)  
8 <sup>38</sup>. TMS-induced responses were obtained by subtracting the individual time-domain average  
9 from each trial before calculating the TF of the single trials <sup>39</sup>. We performed single-trial  
10 normalization by z-transforming the TF of each trial for each frequency. The z-transformation  
11 was based on the respective mean and standard deviation derived from the full trial length.  
12 This was followed by an absolute baseline correction for each trial, by subtracting the average  
13 of the 100 to 50 ms period for each frequency to ensure z-values represented a change from  
14 pre-TMS baseline.

15 At the end, we had an array of 61 x 42 x 201 elements (61 channels, 4 Hz to 45 Hz with  
16 frequency resolution of 1Hz, and data starting from -1000 to +1000 ms with time step of 10  
17 ms). Note that, to minimise TMS and DC shifts effects along the time (3<sup>rd</sup> dimension) and  
18 frequency (2<sup>nd</sup> dimension) axes, we selected the data starting from 40 ms after the TMS pulse  
19 to 1000 ms after the TMS pulse and frequency bins between 4 to 34 Hz resulting in a new 3D  
20 array of 61 × 31 × 98 elements. These steps were repeated for all segments and all channels.

### 21 *2.3.2 Tensorisation of TMS-EEG data and PARAFAC modelling*

22 The TMS-EEG data construction described in section 2.3.1 resulted in a three dimensional  
23 tensor [channel (or space) × frequency × time], representing a time varying spectrum of all  
24 channels. Tensors are multi-dimensional data arrays that extend vectors (one dimensional)  
25 and matrices (two dimensional) to more than two dimensions <sup>11,12</sup>. This three-dimensional  
26 tensor [channel (or space) × frequency × time] will be used in our subsequent tensor  
27 decomposition based analysis. Figure 1 illustrates the principle of tensor decomposition  
28 based on the PARAFAC model for our tensorised TMS-EEG data (as a 3D tensor for simplicity).



1 Assuming that we have a 3D tensor  $\mathbf{W}$ , this data array can be approximated as a sum of  $N$   
2 rank-one tensors, which represent underlying components<sup>17,40</sup>. Each component is an outer  
3 product of three matrices ( $\mathbf{A}$ ,  $\mathbf{B}$  and  $\mathbf{C}$ ) as:

$$4 \quad w_{ijk} \approx \sum_{r=1}^n a_{ir} \cdot b_{jr} \cdot c_{kr}, \quad (1)$$

5 where  $w_{ijk}$  is an element in the tensor  $\mathbf{W}$ , which is approximated by the summation of  $N$  rank-  
6 1 components which are the outer product of  $a_{ir} \cdot b_{jr} \cdot c_{kr}$ , where, for example,  $a_{ir}$  is an  
7 element in the matrix  $\mathbf{A}$  which contains the profiles of the extracted components along the  
8 first dimension (channel or space). Likewise,  $\mathbf{B}$  and  $\mathbf{C}$  contains the estimated components  
9 along the second (frequency) and third (time), respectively, see Figure 1 (A and B). This data  
10 model assumes that the neural generators resulting in the scalp EEG activity are stationary  
11 during the recording period.

### 12 2.3.3 Selecting the optimum number of components

13 There is no a priori means to determine how many components will best represent the data.  
14 Explained variance were used to help estimate an appropriate number of components in  
15 PARAFAC.

16 To estimate the optimal number of **components**, we decomposed a 5D tensor (consisting of  
17 all conditions from all subjects [ $61 \times 31 \times 98 \times 13 \times 6$  elements]) into a different number of  
18 components ranging from one to eight ( $n=1,..,8$  in equation 1), and estimated the explained  
19 variance in each instance. The selection of a relatively low number of components reduces  
20 the chances of overfitting and facilitates its interpretation. More importantly, the  
21 topographical, temporal and spectral profiles of the extracted components were inspected to  
22 determine a number of PARAFAC components that would aid in the interpretation of the data.  
23 It is important to inspect the profiles of components extracted for each considered value of  
24  $n$  since it is not guaranteed that the components extracted when computing PARAFAC with  
25  $n-1$  will appear again when doing so with  $n$  components<sup>13</sup>.

26 **Besides estimating the explained variance, we also estimated the core consistency diagnosis**  
27 **(CORCONDIA, see the supplementary section A2)<sup>41</sup>. CORCONDIA is a heuristic measure to**  
28 **check if the data can be modelled fully multilinearly.**

#### 1 2.3.4 Using tensor decomposition to characterise and contrast effects of AEDs and placebo

2 Building on the 3D tensor described above, we constructed a five dimensional tensor  
3 consisting of the three previously described dimensions (space, frequency, time) and adding  
4 two further dimensions, subject and condition (see Figure 2), by stacking 3D tensors obtained  
5 from section 2.3.2 in order to account for all the interactions of space, time and EEG  
6 oscillation frequency with the effects of drugs on the subjects. We then tested the effects of  
7 drugs on the subjects by contrasting conditions in four different ways, and including these  
8 conditions in the 5<sup>th</sup> dimension (condition):

9 Model 1: We also use this model as a proof of concept to study the components obtained  
10 from PARAFAC without any effect from drug in order to validate the tensor decomposition  
11 of TMS-EEG data.

12 Model 2: To test the hypothesis that levetiracetam and lamotrigine have different effects,  
13 we included four conditions: pre-LEV, post-LEV, pre-LTG, post-LTG.

14 Model 3: To test the hypothesis that levetiracetam has a different effect than placebo, we  
15 included four conditions: pre-placebo, post-placebo, pre-LEV, post-LEV.

16 Model 4: To test the hypothesis that lamotrigine has a different effect than placebo, we  
17 included four conditions: pre-placebo, post-placebo, pre-LTG, post-LTG.

18 These four separate models allow us to first validate the application of PARAFAC to TMS-EEG  
19 data and then to compare in pairs the effect of each drug between them and versus placebo  
20 in data-driven, unsupervised way. Considering the post processed data (3D tensors) obtained  
21 from step 2.3.2, for each subject (per condition) we had a data array of  $61 \times 31 \times 98$  elements.  
22 After stacking these 3D tensors from all subjects for the specific conditions as described in  
23 each model, we obtained a 5D tensor of  $61 \times 31 \times 98 \times 13 \times 4$  elements. Unlike the example  
24 in Figure 1, showing the decomposition of the 3D tensor, with the newly constructed 5D  
25 tensor we could decompose this 5D array into a sum of 5 rank-one tensors (space (or  
26 channel), frequency, time, subject, and condition).

27 In this study, we used the N-way toolbox version 3.3 for tensor decomposition <sup>42</sup>  
28 (<http://www.models.life.ku.dk/nwaytoolbox>). Note that we applied the non-negativity  
29 constraint to all dimensions while performing decomposition. Thus every element in the

1 decomposed arrays would be at or greater than zero <sup>14,17,43</sup>. This constraint was imposed for  
2 a ease of interpretation.

### 3 *2.3.5 Statistics*

4 We applied a permutation based analysis to test for significant difference between pre-vs-  
5 post drug. All steps taken are presented as follows (see the graphical representation of all the  
6 steps in the supplementary Figure A1). At each model, we first decomposed the 5D tensor  
7 (with 61 x 31 x 98 x 13 x 4) into three components. These components were considered as  
8 'master' components (that is, the 'true labelled' components, in distinction to permuted  
9 components, see below). Each of these components consisted of five profiles across the five  
10 dimensions (axes). For example in model-1, at each component we obtained five rank-1  
11 tensors with 61, 31, 98, 13, and 4 elements for space, frequency, time, subject and condition,  
12 respectively.

13 Then we permuted this 5D tensor for 1,000 iterations. At each iteration, we permuted the  
14 elements on the 4<sup>th</sup> and 5<sup>th</sup> dimensions (subjects and conditions). Next, we decomposed this  
15 permuted 5D tensor while fixing all elements in the first three tensors. From this step, we  
16 obtained a new set of five rank-1 tensors, where the first three tensors (representing space,  
17 frequency and time) were similar to the ones in the master, but the elements in the 4<sup>th</sup> and  
18 5<sup>th</sup> tensors could be different from the master because shuffling the data along those  
19 dimensions destroys the inherent structure.

20 To assess the effects after drug/placebo intake, we subtracted the value on the 5<sup>th</sup> dimension  
21 of the pre drug from the value post drug. For example, considering the 2<sup>nd</sup> component of the  
22 master (true label), we subtracted the value before LEV intake from the value after LEV intake  
23 see the supplementary Figure A1). For the permuted data, at each iteration we estimated the  
24 level of change post drug as we did with the master. Then, we computed a histogram of these  
25 values. The level of change in master (true label) was significant if its value was less (or  
26 greater) than 2.5% of the distribution of the histogram. Note that the green square in the  
27 histogram at the bottom right of the supplementary Figure A1 represents the difference  
28 between pre-vs-post LEV, where the two red vertical lines represent the upper and lower  
29 2.5% of the histogram.

### 30 *2.4 Data and code availability statement*

1 Data and code are available upon request.

## 2 **3. Results**

### 3 *3.1 Optimum number of decomposed components*

4 We first explored our data to determine the optimal number of components. We  
5 decomposed the 5D tensor (space, frequency, time, subject, condition) build from all subjects  
6 and all six conditions into a range of number of components from one to eight. First, we  
7 showed the percentage of explained variance at different number of components in Table 1.  
8 Then, we showed the topographical, temporal and spectral profiles of the extracted  
9 components from all eight cases (see the supplementary Figures A2-A4).

10 From Table 1, a marked change was found in these parameters when increasing the number  
11 of components from one to three: i.e. ~10% increase in terms of explained variance. Above 4  
12 components, further increasing the number of components did not significantly change either  
13 of these parameters.

14 In the supplementary Figure A2, representing the decomposed components on the 1<sup>st</sup>  
15 dimension (space), we found three typical underlying spatial patterns (highlighted in green,  
16 red and blue), which were relatively consistent (at least 6 out of 8 scenarios).

17 Moving on to the frequency axis (2nd dimension), if we decomposed the 5D tensor into a  
18 single component, this component would be represented primarily in the alpha range, see  
19 the supplementary Figure A3. When decomposing the same 5D tensor into two components,  
20 a component primrily in the theta frequency range was found in addition to the alpha  
21 component. Decomposed into three components, we observed they were distinct, primarily  
22 in theta, alpha and beta bands. After that, increasing the number of components did not add  
23 any other distinct components at other frequency bands, as most of the further decomposed  
24 components overlapped with the components found when decomposed into just three.

25 Finally, in the time axis unlike the first two axes it was harder to justify a number of  
26 independent components. By visual inspection, at least three distinct components were  
27 found, see the supplementary Figure A4.

1 Taking these together, we decided to decompose the 5D tensor into three components where  
2 the three distinct frequency band and three unique spatial patterns were clearly observed  
3 and the explained variance reached its plateau at about 40%.

#### 4 *3.2 Comparison across the four models*

5 Figure 3 shows three components decomposed from our four different models. The 5D tensor  
6 from each model was decomposed into three components at three different frequency bands  
7 (theta, alpha, and beta, see the 2<sup>nd</sup> column in Figure 3).

8 The model 1 is a proof of concept showing the three physiological components (beta, alpha  
9 and theta) decomposed from the TMS-EEG data without any effect from LEV or LTG.

10 First considering the beta components (labelled in blue) from all models, these components  
11 mostly represented frontal brain activities. On the time axis (3<sup>rd</sup> dimension), each of these  
12 beta components could be divided into 3 phases: (1) initial peak (during 40 – 200  
13 milliseconds), (2) suppression (200 – 400 milliseconds) and (3) rebound (400 milliseconds  
14 onward). When we compared between models 3 and 4 (between LTG and LEV), one could  
15 observe less rebound of this beta component in LTG as compared to LEV.

16 The next component, which was predominantly observed in alpha range, showed the most  
17 variability (in terms of magnitude and spatial pattern) among the three components (theta,  
18 alpha, and beta) across all models. Whereas one could see the alpha component dominating  
19 occipital lobe in models 2 and 3, in model 4 this alpha activity can be seen everywhere (with  
20 high amplitude) except on the areas next to the earlobes.

21 Moving on to the last component, or theta labelled in orange, it was spatially identical across  
22 all models and represented the activities on C3. This component reached its peak around 200  
23 milliseconds and completely suppressed starting ~400 milliseconds to the end of each  
24 recording.

#### 25 *3.3 Model 2: comparison of the effects of levetiracetam and lamotrigine.*

26 Figure 4 shows the three decomposed components in five dimensions, which were  
27 highlighted in blue, red and orange for 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> components respectively. The first  
28 component (blue) represented the brain activities (in the beta range, peak at 19 Hz) over the  
29 frontal and central areas. On the time axis (3<sup>rd</sup> dimension), this component initially peaked at

1 ~90 milliseconds after applied TMS pulse, then suppressed between 190 – 400 milliseconds,  
2 and rebounded from 440 milliseconds to the end of the recording.

3 The second component (red) represented the activities with relatively lower frequency (at  
4 alpha band or between 6 - 13 Hz), which predominantly involved the occipital lobe. Initially,  
5 during 40 – 140 milliseconds after the TMS pulse, while the 1<sup>st</sup> component (frontal beta) was  
6 reaching its peak, this component (occipital alpha) was absent. Subsequently, during 140 –  
7 340 seconds, while the 1<sup>st</sup> component was declining and eventually completely diminished,  
8 this 2<sup>nd</sup> component was on the rise and reached a plateau. Starting from 440 milliseconds  
9 until the end of the recording, these two components coexisted.

10 The last component (3<sup>rd</sup>, orange) was found in the theta band (4-6 Hz), centered on EEG  
11 electrode C3, which was the location where the TMS pulses were given. This component  
12 reached its peak between 90 – 240 milliseconds, and later was suppressed starting from 440  
13 milliseconds until the end of recording (which was the period where both 1<sup>st</sup> and 2<sup>nd</sup>  
14 components coexisted).

15 Inter-subject variabilities were revealed in the 4<sup>th</sup> dimension showing the 1<sup>st</sup> , 10<sup>th</sup> and last  
16 subject being different from the others. On the 5th dimension condition (drug) effects were  
17 revealed, and we observed reduction in all components after receiving medication (both LEV  
18 and LTG). From this plot, one could see a stronger post medication effect for LEV as compared  
19 to LTG, especially in the 2<sup>nd</sup> component. At a group level, there was a significant effect of  
20 reduction of the 2<sup>nd</sup> component after LEV intake (see Figure 5).

### 21 3.4 Statistics

22 Figure 6 shows distributions of difference between pre-and-post medication from 1000  
23 iterations in models 2, 3 and 4. Statistically, no significant change in either theta or beta  
24 components was found (see columns 1 and 3). Considering models 3 and 4, when we  
25 investigated the effects after drug vs after placebo, we found significant reduction of alpha  
26 component in both post LEV ( $p=0.015^*$ ) and post LTG ( $p=0.021^*$ ) conditions. In model 2,  
27 when we compared the effects after drug intakes in both LEV vs LTG, the post-LEV shows a  
28 significantly stronger reduction of the alpha component than post-LTG with  $p=0.01^*$ .

29

## 1 4. Discussion

2 In this study, we introduced a tensor decomposition method to reduce multi-dimensionality  
3 of TMS-EEG data. We showed a series of components which provides a parsimonious  
4 description of neurophysiological responses underlying TMS-induced oscillations. In addition  
5 we demonstrated the utility of PARAFAC on existing data to disentangle the effect of anti-  
6 epileptic drugs on TMS-induced oscillations. This method does not require *a-priori* selection  
7 of anatomical regions of interest, time periods of interest and frequency components of  
8 interest in the multi-dimensional EEG data, and without requiring potentially harsh post-hoc  
9 statistical correction for multiple comparisons. PARAFAC revealed an effect of both  
10 levetiracetam and lamotrigine, significantly suppressing oscillations in the alpha range in the  
11 occipital region, during the time period approximately 140 ms - 840 ms after the TMS pulse.  
12 Furthermore, this technique also reveals that the suppression of alpha oscillations is  
13 significantly stronger during the intake of levetiracetam than lamotrigine.

### 14 4.1 Optimum number of decomposed components and justification of PARAFAC model

15 From Table 1, the explained variance in the data reached its plateau when splitting into three  
16 components. This suggests three as the optimal components. To justify our choice, we also  
17 visually inspected the decomposed profiles on space, time and frequency axes  
18 (supplementary Figures A2 – A4). This is important as the profiles of components extracted  
19 for each considered value of  $n$  since it is not guaranteed that the components extracted when  
20 computing PARAFAC with  $n-1$  will appear again when doing so with  $n$  components<sup>13</sup>. The fact  
21 that similar patterns appeared naturally provides further support to the interpretability of our  
22 chosen model. The inspection of the components also enabled us to grasp which physiological  
23 processes captured by the data-driven components were prominent in the TMS-EEG  
24 recordings. The results support our choice of 3 components. It was clear that along the  
25 frequency axis (supplementary Figure A3) regardless of the number of decomposed  
26 components we could only break down into maximum three different frequency bands  
27 (theta, alpha, and beta). Moving on to the spatial axis (the supplementary Figure A2), it was  
28 debatable if a maximum number of components could be either three or four. Finally, along  
29 the time axis (the supplementary Figure A4), the optimal number of component was unclear  
30 (it could either be any number between two to four). Looking at the CORCONDIA in the  
31 supplementary Table A2, we found that by extracting more than one component the value of

1 CORCONDIA drop to zero. This suggests our 5D tensor is not a fully multilinear form and also  
2 explains the non-equivalent number of optimal components along different axes <sup>41</sup>. Taking all  
3 these together, we then decided to decompose into three components, where all three  
4 unique signatures along frequency and spatially domains were found, and the explained  
5 variances reached its plateau. It is important to note that the explained variance may not  
6 increase significantly with the number of components since the multilinear PARAFAC model  
7 will not explain the noise and random variations in the data. Furthermore, increasing the  
8 number of components would lead to higher computational cost <sup>44</sup>.

9 Although another family of tensor decompositions (Tucker decomposition) may provide a  
10 solution to the case with a non-equivalent number of optimal components, it does not  
11 preserve one-to-one interaction <sup>33,45</sup>. Hence, the decomposed components using Tucker  
12 decomposition are harder to interpret. To sum up, we decided to decompose the TMS-EEG  
13 5D tensor using PARAFAC, which preserves one-to-one interaction. That is each component  
14 will be entitled to a unique interpretation, for example, the TMS induced component may be  
15 seen in a particular frequency range, anatomical distribution and time period. Future work will  
16 explore the suitability of other more flexible, but still unique models such as PARAFAC2 <sup>21</sup>, to  
17 improve the modelling of TMS-EEG data and reveal even more subtle interactions.

#### 18 4.2 Physiological meanings behind the three components

19 From model 1 (without drug) we found three physiological components (theta, alpha and  
20 beta), these components are highly similar (spatially, temporally and spectrally) across four  
21 models, see Figure 3. Given that the PARAFAC solution is unique under very mild conditions,  
22 this further reinforces that the extracted components have physiological meaning. These  
23 components (frontal-sensorimotor beta, posterior alpha and theta related to the site of  
24 stimulation) represented the hidden signature of the data for all conditions (pre/post PLA,  
25 pre/post LEV, pre/post LTG). We considered the frontal-sensorimotor beta component to  
26 represent the spreading of cortical reactivity from the stimulated site (C3) through its  
27 neighboring areas via local fibers as well as to the contralateral motor cortex via corpus  
28 callosum <sup>46</sup>. Sensorimotor rhythms, which dominate the motor cortex, are found in mu (8-13  
29 Hz) and beta rhythms (15-30 Hz) <sup>47,48</sup>. By giving a TMS pulse, it may elicit similar effects on the  
30 cortical neurons seen as event-related (de)-synchronization (ERD/ERS) time locked to motor  
31 movement over motor cortex areas <sup>49-51</sup>. Since the rebound of sensorimotor rhythms



1 (synchronization) is uniquely observed in the beta range after giving stimuli <sup>49,50</sup>, by imposing  
2 the non-negativity constraint to the 5D tensor we might limit the decomposed component at  
3 this area only in the beta band. Moving on to the posterior alpha, it is found to be a key  
4 component shown to differentiate between the two drugs, seen as the stronger reduction of  
5 alpha component after LEV compared to LTG intake, in model 2. Considering both models 3  
6 and 4 (placebo vs each type of drug), we found the significant reduction of this component  
7 after both LEV and LTG intake (whereas no change was found post placebo). Results suggest  
8 that both types of drug cause similar effects on the generation of posterior alpha. The same  
9 observation derived from the investigation of these AEDs on TEPs, where despite the varying  
10 profile of effects and regardless of the (putative) molecular targets of the different drugs,  
11 systemically administered LEV and LTG exert similar modulation of TEPs (Premoli et al 2017).  
12 In addition, the effect on alpha was stronger under LEV exposure which had the highest  
13 average concentration in blood outside the reference range, with LTG averaging toward a  
14 lower concentration for its reference range (Premoli et al 2017).

15 Lastly, considering theta, this component represents the TMS-induced effect on the  
16 stimulation site, because its spatial pattern was centred on C3 and its temporal signature  
17 shows a peak soon after stimulation and then subsided.

18

#### 19 4.3 Strengths and weaknesses of this study

20 Unlike a conventional TMS-EEG analysis, which requires predefining time, anatomical area  
21 and frequency of interest, tensor decompositions offer a purely data-driven approach. In  
22 particular, we applied PARAFAC due to its parsimony and ease of interpretation since the  
23 interactions of the components are restricted. In our analysis, the 5D tensor for each mode  
24 had dimensions  $61 \times 31 \times 98 \times 13 \times 4$  (9,636,536 entries in total). Decomposing it with  
25 PARAFAC, the method was able to account for approximately 40% of the explained variance  
26 with just 3 components which include only 621 elements – i.e.,  $3 \times (61 + 31 + 98 + 13 + 4)$ , less  
27 than 0.01% of the total number of entries in the tensor. The results were tested under  
28 permutation-based statistics. We successfully showed that each decomposed component  
29 represents the unique signature on the spatial, spectral and temporal domains with  
30 physiological meaning. Furthermore, along the 4<sup>th</sup> dimension, one could make the inference

1 about these hidden signatures at a single subject level. Despite the positive results provided  
2 by this innovative analysis approach of TMS-EEG data, it must be taken into consideration that  
3 the TMS pulse can induce unwanted somatosensory input that has an impact on TEPs<sup>52</sup>. We  
4 purposely selected a PARAFAC model with non-negativity constraints to simplify the  
5 interpretation of the components extracted from TMS-EEG activity in this first application of  
6 tensor decompositions to this type of data. However, we acknowledge that the choice of the  
7 non-negativity constraint implies that we were not able to reveal potential patterns in  
8 negative values and that our results are also limited by the small number of participants and  
9 we advise the reader to interpret them with care.

## 10 **5. Conclusion**

11 To our knowledge, it is the first time tensor decomposition has been applied in TMS-EEG data.  
12 Our results show the power of tensor decompositions to reveal the profiles underlying the  
13 complex responses in TMS-EEG data associated with different AEDs in healthy subjects in a  
14 data-driven and parsimonious way. Future work will seek to develop classifiers able to predict  
15 the level of response to each AED in new subjects by projecting their TMS-EEG recordings on  
16 the “characteristic filters” associated with previously revealed tensor components in space,  
17 time and frequency<sup>26,53</sup>. We will also consider the possibility of applying tensor  
18 decompositions to TMS-EEG signals in the time domain following other previous applications  
19 of these techniques to event-related EEG activity<sup>14</sup>.

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25

## 26 **Contributions**

27 MR, JE and RC designed and supervised the research. IP collected and preprocessed the data. CT and  
28 LS wrote the analysis scripts. CT analysed the data. CT, IP and JE wrote the manuscript. All authors  
29 reviewed the manuscript.

## 1 Conflicts of interest

2 The authors **declare** that there is no conflict of interest.

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1 Table 1: Percentage of explained variance by a number of decomposed components

Scenario	No. of Components	Explained variance (%)
I	1	29.14
II	2	34.06
III	3	39.33
IV	4	41.21
V	5	42.53
VI	6	43.49
VII	7	44.05
VIII	8	44.03

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## 1 List of Figures

2 Figure 1A shows  $N$  decomposed components from the 3D tensor  $\underline{W}$ , each component comprises three  
3 vectors (A, B and C). Figure 1B shows an example when the technique was used to decompose the 3D  
4 (space x frequency x time) of subject#2 post LEV. In this case, the three components represent high,  
5 medium and low-frequency ranges (15-30 Hz "Beta", 6-13 Hz "Alpha", and 4-6 Hz "Theta". The bottom  
6 two insets show a Space-vs-Frequency plot at 150 milliseconds after TMS pulse and its grand average  
7 across all channels.

8 Figure 2: The five-dimensional tensor in this study comprises of space (channel), frequency, time,  
9 subject and condition (1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> dimension, respectively).

10 Figure 3: We present the three components decomposed from 5D tensor in four different models. The  
11 top row shows the decomposed components in space (topographical plots), frequency and time  
12 dimension. Three colours (blue, red and yellow) are used to indicate the three decomposed  
13 components: beta (with peak frequency between 15-30 Hz), alpha (with peak frequency between 6-13  
14 Hz) and theta (with peak frequency between 4-6 Hz), respectively.

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16 Figure 4: The three components decomposed from the 5D tensor in all subjects during pre-drug and  
17 post-drug conditions with LEV or LTG. Note that: D stands for Dimension.

18 Figure 5: Each histogram shows the distribution of strength on the 5<sup>th</sup> dimension obtained from 1000  
19 iterations of permutation. Two vertical red lines indicate the upper and lower 2.5% of the histogram.  
20 Each green square indicates the difference between pre and post medication on the 5<sup>th</sup> dimension. In  
21 the top and bottom rows (showing the results from components 1 and 3, respectively), no significant  
22 reduction was found. For component #2 (middle row), we observed the significant reduction in terms  
23 of strength on the 5<sup>th</sup> dimension after receiving LEV.

24 Figure 6: Each histogram shows the distribution of difference between pre and post medication (or  
25 placebo) from 1000 iteration. The two red lines in the histograms indicate the first and last 2.5 percent.  
26 The green square represents the post vs pre difference on the 5<sup>th</sup> dimension. \* denotes significant  
27 ( $P < 0.025$ ). All histograms on the top, middle and bottom rows are the distribution from model 2, 3,  
28 and 4, respectively. Note that all the p-values in this study are reported in the supplementary Table A1.

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