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CortExTool: a toolbox for processing motor cortical excitability measurements by transcranial magnetic stimulation

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Abstract

Assessing motor cortical excitability (CE) is essential in transcranial magnetic stimulation (TMS) in order to ensure both safe and normalised stimulation power across subjects or patients. However, there is still a lack of automatic and easy-to-use tools for analysing the electromyographic (EMG) signal features that are relevant for CE assessment, such as the amplitude of motor evoked potentials (MEPs) or the duration of cortical silent periods (CSPs). Here, we describe CortExTool, a signal processing toolbox we developed to fulfil these needs. The toolbox, developed in the Matlab programming language, is open-source and freely accessible to the TMS community. CortExTool provides all the standard functionalities required to automatically process EMG signals recorded during a CE experiment, on both individual and group levels. Its use should allow to standardize and to facilitate the processing of CE measurements by TMS.

Keywords: EMG processing toolbox, TMS, Cortical excitability, MEP, CSP

1. Background

Transcranial magnetic stimulation (TMS) is a noninvasive cortical stimulation technique, which is now widely used in both fundamental and clinical research (Rossi et al., 2009; Sandrini et al., 2011; Lefaucheur et al., 2014). Assessing cortical excitability (CE) on the motor cortex, by estimating the motor threshold (MT), is a mandatory step prior to any TMS experiment. Stimulation intensities are always expressed as a percentage of this threshold, in order to conform to safety guidelines and to normalise the stimulation power between subjects (Rossi et al., 2009; Herbsman et al., 2009; Lefaucheur et al., 2011). Motor CE measurement is based on the feature analysis of motor evoked potentials (MEPs), such as amplitude and latency, recorded on the electromyogram (EMG) of the targeted muscle (Wassermann, 2002; Säisänen et al., 2008; Littmann et al., 2013). CE can also be used as a biomarker of various cognitive states (Beynel et al., 2014) and psychiatric disorders (Malsert et al., 2012; Radhu et al., 2013), when completed with the evaluation of cortical inhibitory and excitatory circuits through paired pulse stimulations (Roshan et al., 2003; Stagg et al., 2011) and/or with the measurement of the cortical silent period (CSP) (Fuhr et al., 1991).

Major technical progress has been made in the practice of TMS over the last decade (Gugino et al., 2001; Kantelhardt et al., 2009; Finke et al., 2008; Grau et al., 2014). However, there is still a lack of practical and easy-to-use software solution regarding off-line processing of EMG signals resulting from CE measurements. We therefore developed a new signal processing toolbox CortExTool, dedicated to CE measurement. This toolbox allows automatic processing of MEP data in order to quantify standard CE features in a fast and user-friendly way.

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2. Toolbox description and functionalities

2.1. Overview

CortExTool is a free toolbox (under the GNU General Public License v3) implemented in Matlab (*The MathWorks Inc., United States*). It is based on a simple graphical user interface showing all the toolbox functionalities in a single window (Figure 1A). Every signal processing function (see 2.3, 2.4) is easily accessible via push buttons, lists, check boxes, and menu entries. Functions can be applied either on experimental conditions or on individual trials. Whenever necessary, appropriate data or results are automatically displayed. Results can be obtained both at individual and group level.

Data are processed as follows. The EMG signals are first loaded into the toolbox, then preprocessed using band-pass filters, artefact removal, and MEP/CSP automatic detection. The signal features can finally be viewed and processed in several ways, and/or be exported for further statistical analysis.

2.2. Input data

For now, CortExTool is compatible with data coming from Keypoint (*Natus Medical Inc., United States*), Spike2 (*Cambridge Electronic Design Limited, England*) EMG recording systems, and any data exported in European Data Format (EDF and EDF+). Data has to be arranged within one folder per unique subject, containing one subfolder per condition or experimental block (see details in the user-guide documentation).

2.3. Preprocessing

Filtering

Data are automatically filtered when loaded in the toolbox using a 5-600 Hz Butterworth band-pass filter, encompassing the frequency range of the EMG activity (Komi and Tesch, 1979; De Luca et al., 2010).

Automatic artefacts detection

Since the muscular contraction level of the pre stimulation period is highly correlated with some MEP features such as amplitude (Darling et al., 2006), it has to be controlled in protocol involving resting condition. Any trial showing a pre-stimulus contraction should then be considered as artefacts. Automatic artefact detection is based on the analysis of the pre-stimulation period, if available in the data. The root mean square power (RMS) of the EMG signal RMS_b is computed in the time window preceding the stimulation onset. Any trial whose corresponding RMS_b exceeds a certain threshold is then considered as an artefact. This threshold is tunable ($500\mu V$ by default) and its optimal value depends on the recorded muscle and the EMG system recording parameters used (gain, filters, etc.). Trials can also be manually marked as artefact. Users can finally choose to discard any trial marked as artefact from further analysis.

MEP detection

MEPs are automatically detected and labelled using four markers: beginning (t_{start}), end (t_{end}), and local extrema t_1 and t_2 of the MEP (Figure 1B). A cross-correlation function $s_f * u$ between the filtered signal $s_f(t)$ and an EMG template $u(t)$ representing a typical MEP (see below) is computed. Local maxima $m_{1:N}$ and their corresponding time indices $t_{m_{1:N}}$ are then extracted from the cross-correlation function $s_f * u$. Each maximum represents a possible location of the MEP in the EMG signal. Maxima are then sorted in descending order and sequentially processed according to the following algorithm.

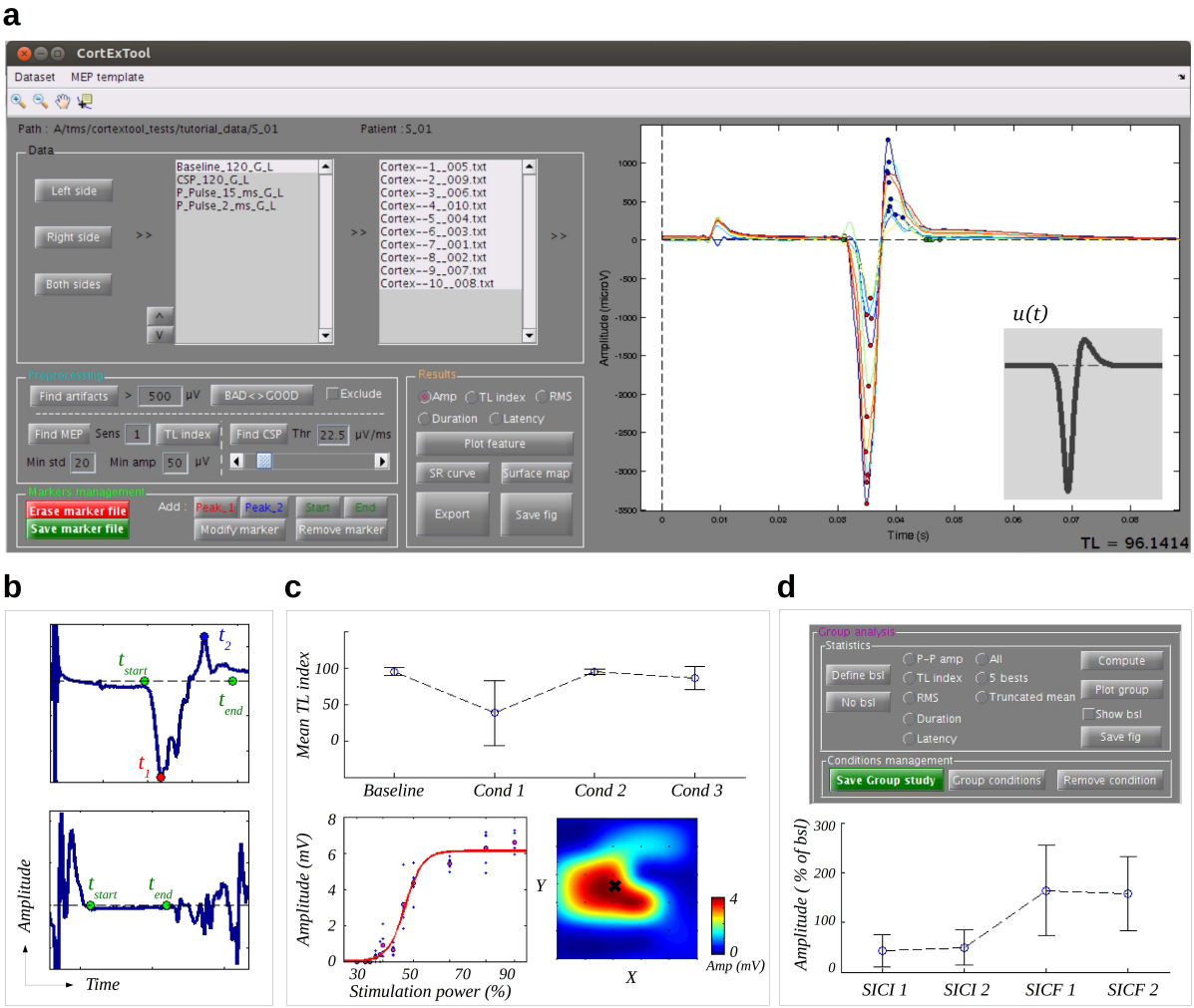

Figure 1: CortExTool General User Interface (GUI) and its main functionalities. A - CortexTool GUI. Bottom right grey insert: default FDI template $u(t)$. B - Preprocessing panel: results of automatic MEP (top) and CSP (bottom) detection. Markers t_{start} and t_{end} are displayed in green, while t_1 and t_2 are coloured in red and blue respectively (see 2.3). C - Results panel, from top left to bottom right: means of the selected feature (here, TL index) across conditions, S-R curve, and surface map. D - Group level panel, from top to bottom: GUI, plot of peak-to-peak amplitude means in percentage of the defined baseline across conditions.

For the ith maximum:

1. List first local minima and maxima indexes t_1 and t_2 of $s(t)$ surrounding m_i
2. Test whether
   - $|s(t_1)-s(t_2)| > A_{min}$,
   - $std(s(t_{m_i} \pm w)) > \theta_{std}$,
   - $|t_1 - t_2| \in [w \pm kw]$,

   with w being the time interval between the corresponding maxima and minima of u, std being the standard deviation operator, and A_{min} corresponding to the minimum amplitude of the MEP (tunable, $50\mu V$ by default). θ_{std} and k are the minimum standard deviation and sensibility parameters respectively. These parameters prevent false alarm by checking the width and the surrounding EMG activity level of the detected MEP. Their default values are $20\mu V$ and $1(AU)$ respectively.
3. If one of those tests is false, iterate $i = i + 1$ and return to step 1, otherwise stop and set MEP peaks at t_1 and t_2 respectively.

Temporal boundaries of MEP are then found using the calculation of the surrounding standard deviation. Rise and fall of this value (found by thresholding of the first derivative) correspond to the beginning and the end of the muscle contraction.

By default, the toolbox uses a template of the first dorsal interosseous muscle (FDI). This EMG template was generated by averaging 1959 baseline MEPs of the FDI muscle coming from 49 different subjects of our own TMS experiments database (grey insert in Figure 1A - see 3). The algorithm can also handle other templates coming from any other muscles. A simple tool is provided within the toolbox to build other templates from recorded data. As a consequence, the toolbox can be turned into a detector of any particular signal, as long as it can be defined by a stereotypical shape.

CSP detection

CSPs are automatically delimited using two markers: beginning (t_{start}) and end (t_{end}) of the induced muscular atonia (Figure 1B). The automated CSP detection algorithm is based on the thresholding of the first derivative of the epoched signal. The CSP is then defined as the duration between t_{start} and t_{end}, for which the first derivative is under this threshold (see Julkunen et al. (2013) for the detailed routine). The threshold value is $22.5\mu V/ms$ by default, as proposed by Julkunen et al. (2013), but remains adjustable by users.

2.4. Analysis function

EMG features

Five features can be extracted from analysed EMGs. The means and standard deviations of the selected features can then be plotted across conditions in the visualisation window (Figure 1C). The features are:

- latency (in ms), expressing the delay between the stimulation onset and t_1 for MEP or t_{start} for CSP,
- duration (in ms) being the time between t_{start} and t_{end},
- amplitude (in μV) representing the peak to peak amplitude of the signal at t_1 and t_2,
- mean RMS (in μV) calculated as the RMS averaged between markers t_{start} and t_{end},
- template likeness (TL) index (in %), defined as:

$$TL = \max(s(t_{min} \pm \frac{w}{2})' * u) \times 100 \tag{1}$$

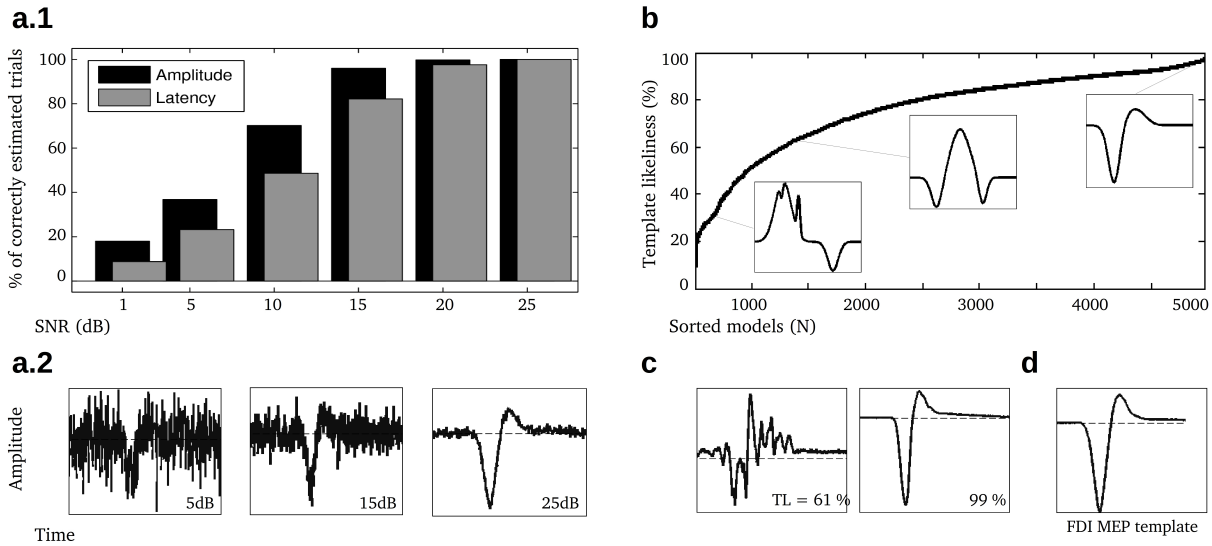

Figure 2: Results of automated MEP detection and evaluation of Template likeliness. A.1 - Percentage of trials correctly estimated in terms of amplitude and latency across SNR values. A.2 - Examples of simulated MEPs for SNRs of 5, 15, and 25 dB. B - Gaussian mixture models sorted by TL. Individual boxes show examples of simulated data for TL indexes of 30, 60, and 95%. C - Examples of real MEPs showing TL indexes of 61 and 99%. D - FDI MEP template $u(t)$ used by default.

with u being the MEP template, s' the re-sampled MEP signal so that the time interval between t_1 and t_2 (see 2.3) equals the one of u, and $*$ the normalized cross-correlation product.

TL indicates the shape similarity between the analysed MEP and the template. Since the toolbox allows users to generate their own EMG template (see 2.3), this indicator can be turned into a likeness index of any other MEP or signal shapes. For example, this could be useful while trying to detect signal irregularities in a patients *vs* controls paradigm. Since the surface EMG results from the summation of motor unit action potentials (MUAPs), their synchronization generates high amplitude EMGs shaped like MUAPs (Yao et al., 2000). If the template's waveform stays closed to underlying MUAP shapes, as for our default template (Kleine et al., 2000; Zhou et al., 2001; Luca et al., 2014), see 2.3 and Figure 2d), TL will be a direct indicator of the MUAPs synchronisation level.

Stimulus-Response curve

Stimulus-Response (S-R) curves (Ridding and Rothwell, 1997) can be visualized (Figure 1C) once having defined the stimulation powers used to obtain the selected MEPs. A non-linear fitting function (*nlinfit* matlab function) then estimates the sigmoid curve linking all the MEP amplitudes, using the following parametric function:

$$f_{SR}(t) = |P_1| + \frac{P_4}{1 + e^{(-P_2 * (t - P_3))}} \tag{2}$$

where P_1, P_2, P_3 and P_4 are the four estimated parameters.

Mapping

The toolbox offers the possibility to plot data coming from motor mapping protocols. The spatial pattern of a particular feature can thus be studied, its mean being plotted as a function of the stimulation site coordinates. After having entered the size of the stimulation grid, a 2D image showing the mean selected features according to each spatial node is displayed (Figure 1C, bottom right). Motor maps can be smoothed using a tunable bi-cubic 2D interpolation. The center of gravity (COG) of the map is calculated and displayed through a black cross.

2.5. Group level

Analysis can be conducted on the data of a group of subjects already processed by CortExTool (Figure 1D). Each of the five EMG features (see 2.4) can be analysed across conditions and subjects. Users can define a baseline condition in order to normalize values.

2.6. Output data

All the EMG markers are recorded in Matlab file format in the corresponding analysis folder. Extracted features of each trial can also be exported in spreadsheets for complementary statistical analysis using external softwares. At any time, figures displayed in the toolbox can easily be exported.

3. TMS methods

All the EMGs used for toolbox tests or illustration purposes in this manuscript come from our local database, recorded from healthy volunteers. None had histories of psychiatric illness or neurological disorders, and all were free of any medical treatment likely to modulate cortical excitability. All of them gave a written informed consent. The ethical committee of Grenoble University Hospital (ID RCB: 2012-A00316-37/1 and 2013-A01734-41) approved the studies covering these data.

The data were all recorded at IRMaGE Neurophysiology facility (Grenoble, France) following the same methodology. Electrodes were placed over the subject's first dorsal interosseous muscle in a belly-tendon montage. The EMG signal was amplified (1–10 K), low-pass filtered (6 kHz), and sampled at 12 kHz using a Dantec Keypoint portable system (*Natus Medical Inc., United States*). TMS was delivered using the MC-B65 or the cool B65-RO butterfly coils plugged in a dual-pulse stimulator (MagProX100 MagOption, *MagVenture, Danemark*). The TMS coils were respectively handled by hand or by a TMS-robot (*Axilum Robotics, France*). The TMS coil position was continually tracked using a neuronavigation device (TMS Navigator, *Localite, Germany*). The "hotspot" was defined as the optimal coil position to elicit the greatest motor evoked potential (MEP) in the contralateral muscle. Resting motor threshold (rMT) was then defined using the "threshold hunting" method (Awiszus, 2003) as the minimal stimulation intensity to evoke a $50\mu V$ MEP in fifty percent of trials. MEPs were finally recorded while subjects were at rest following various experimental conditions (depending on the study) including baseline, paired-pulse protocols, CSP measurements, and motor mapping procedures.

4. Evaluation of MEP detection and Template likeliness calculation

We evaluated the performance of our automated MEP detection algorithm and the TL index calculation on simulated data. First, 3000 EMG signals were randomly generated using six different SNR ratios between the MEP template u and a white noise colored in the frequency range of typical EMG signals ($50-400Hz$). Time onset and amplitude of the MEPs were identical for all the generated EMGs. Secondly, 5000 random MEP shapes were computed using a 4-Gaussian mixture model. Several parameters of the model were constrained in order to simulate realistic MEPs.

Figure 2a shows the results of MEP detection on noisy EMG data. The number of correct amplitude and latency estimations increases quickly with the SNR ratio, exceeding 50% between 10 and 15 dB, and 90 % between 20 and 25 dB. Our algorithm has a good performance, since typical recorded MEPs present SNR ratios high above 20-25 dB. The results of TL estimation on simulated MEPs are shown in Figure 2b. As expected, MEPs get a higher TL score when their shape is closest to the template's one. Having more than 2 Gaussians with a non-zero amplitude is penalizing ($TL < 80\%$), whereas MEPs showing the typical asymmetry between the first and second peaks get high values ($TL > 90\%$). Figure 2c shows two examples of real MEPs presenting TL indexes of 61 and 99%.

5. Conclusion

CortExTool is an efficient and easy-to-use tool to process and visualize EMG data coming from CE measurements by TMS. It offers users both fully automated and tunable processing pipelines, allowing the detection of MEPs and CSPs, the extraction of their features, and the display of results on both individual and group levels.

The toolbox is freely available on the corresponding author webpage. User-guides and regular updates are available on the corresponding author webpage. Ongoing developments of the toolbox include the handling of more input formats, the integration of statistical tests, and the software migration to a fully open-source programming language.

6. Conflict of interest

All authors declare no conflict of interest. All authors have approved the final article.

7. Authors contribution

S.H. designed the study, wrote the ethical protocol, recorded TMS data, developed and tested the toolbox, wrote the article. L.B. wrote the ethical protocol, recorded TMS data, tested the toolbox. N.G. recorded TMS data, tested the toolbox. C.M. designed the study, wrote the article. O.D. designed the study, wrote the article. A.C. designed the study, recorded TMS data, tested the toolbox, wrote the article.

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