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Single-trial time–frequency analysis of electrocortical signals: Baseline correction and beyond

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ABSTRACT

Event-related desynchronization (ERD) and synchronization (ERS) of electrocortical signals (e.g., electroencephalogram [EEG] and magnetoencephalogram) reflect important aspects of sensory, motor, and cognitive cortical processing. The detection of ERD and ERS relies on time–frequency decomposition of single-trial electrocortical signals, to identify significant stimulus-induced changes in power within specific frequency bands. Typically, these changes are quantified by expressing post-stimulus EEG power as a percentage of change relative to pre-stimulus EEG power. However, expressing post-stimulus EEG power relative to pre-stimulus EEG power entails two important and surprisingly neglected issues. First, it can introduce a significant bias in the estimation of ERD/ERS magnitude. Second, it confuses the contribution of pre- and post-stimulus EEG power. Taking the human electrocortical responses elicited by transient nociceptive stimuli as an example, we demonstrate that expressing ERD/ERS as the average percentage of change calculated at single-trial level introduces a positive bias, resulting in an overestimation of ERS and an underestimation of ERD. This bias can be avoided using a single-trial baseline *subtraction* approach. Furthermore, given that the variability in ERD/ERS is not only dependent on the variability in post-stimulus power but also on the variability in pre-stimulus power, an estimation of the respective contribution of pre- and post-stimulus EEG variability is needed. This can be achieved using a multivariate linear regression (MVLR) model, which could be optimally estimated using partial least square (PLS) regression, to dissect and quantify the relationship between behavioral variables and pre- and post-stimulus EEG activities. In summary, combining single-trial baseline *subtraction* approach with PLS regression can be used to achieve a correct detection and quantification of ERD/ERS.

Introduction

Sensory, motor and cognitive events not only evoke time-locked and phase-locked changes of ongoing electrocortical signal (e.g., event-related potentials; ERPs and event-related fields; ERFs) (Luck, 2005), but also induce time-locked and non-phase-locked modulations of ongoing oscillatory activity (Neuper and Klimesch, 2006; Pfurtscheller and Lopes da Silva, 1999). These non-phase-locked modulations consist of decreases (event-related desynchronization, ERD) and increases (event-related synchronization, ERS) of oscillatory activity, usually confined to a specific frequency band (Pfurtscheller and Aranibar, 1977; Pfurtscheller and Lopes da Silva, 1999). The functional significance of ERD and ERS varies greatly according to their temporal, spectral, and spatial characteristics (Ohara et al., 2004). For example, ERD in the α band (8–12 Hz) has been hypothesized to reflect cortical activation, whereas ERS in the same frequency band has been interpreted as a reflection of cortical inhibition (Pfurtscheller and Lopes da Silva, 1999). ERD and ERS are extensively used to investigate sensorimotor processes and cognitive tasks, as well as to discriminate neurological disorders and psychometric variables (Fries, 2009; Gross et al., 2007; Neuper and Klimesch, 2006; Pfurtscheller, 1992; Pfurtscheller et al., 1998; Ploner et al., 2006; Schnitzler and Gross, 2005; Singer, 1993).

To measure ERD and ERS, single-trial electrocortical responses in the time domain are usually transformed in time–frequency distributions (TFDs) (Makeig, 1993), which represent signal power as a function of time and frequency, using various time–frequency decomposition methods, such as windowed Fourier transform and continuous wavelet transform (Mouraux and Iannetti, 2008; Zhang et al., 2012). The resulting single-trial TFDs are usually expressed relative to a pre-stimulus reference interval, to highlight stimulus-induced *changes* in oscillation magnitude (Grandchamp and Delorme, 2011). Such baseline-correction procedure is used because it allows identifying sometimes

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subtle stimulus-induced changes of ongoing oscillatory power. It is typically achieved using one of two alternative approaches: (1) *subtraction*, which assumes that ERD and ERS are added onto or subtracted from the existing pre-stimulus power at each frequency, and (2) *percentage* (i.e., subtraction and division), which assumes that ERD and ERS are proportionally decreased or increased with respect to the magnitude of existing pre-stimulus oscillatory power (Grandchamp and Delorme, 2011; Pfurtscheller and Aranibar, 1977). In both approaches the baseline correction can be performed on TFDs at single-trial, single-subject, or group level (Grandchamp and Delorme, 2011; Mouraux and Iannetti, 2008; Zhang et al., 2012). In any of those cases it is important to consider the effect of trial-to-trial (or subject-to-subject) fluctuations in the magnitude of pre-stimulus oscillatory activity on the ERD/ERS estimates. Particularly in the *percentage* approach, which consists in dividing the difference between post-stimulus and pre-stimulus amplitudes by the pre-stimulus amplitude, variations in pre-stimulus amplitude can have a very strong effect on the ERD/ERS estimates. Indeed, if the pre-stimulus amplitude is close to zero, even a very minor increase in amplitude will yield a spuriously high percentage increase. Considering that both pre- and post-stimulus amplitudes are always positive, the distribution of percentage estimates across trials (or subjects) will be highly asymmetrical, with a long tail of extremely high percentage values. Therefore, averaging such percentage values across trials (or subjects) will not provide a meaningful summary measure of ERD/ERS.

Across-trial variability in both pre- and post-stimulus amplitudes may reflect important factors such as changes in the sensory input and time-dependent habituation (Iannetti et al., 2008; Ohara et al., 2004; Stancak et al., 2003), as well as fluctuations in vigilance and expectation (Del Percio et al., 2006; Mu et al., 2008; Ploner et al., 2006). Thus, it is also crucial to dissect the contributions of pre- and post-stimulus power to the variability of ERD/ERS, especially when the trial-to-trial variability of pre-stimulus activity is significant and physiologically relevant (Addante et al., 2011; Salari et al., 2012; van Dijk et al., 2008; Wyart and Tallon-Baudry, 2009). Specifically, when investigating the trial-to-trial relationship between ERD/ERS and behavior variables (e.g., reaction times or intensity of perception), it is important to explore whether such relationship is determined by pre- or post-stimulus electrocortical activity, or both.

In summary, the correct interpretation of the functional significance of ERD/ERS relies on two important but often neglected conditions: (1) the baseline correction procedure should not introduce biases in the estimated ERD/ERS magnitude, and (2) the contribution of pre- and post-stimulus activity on the trial-to-trial ERD/ERS variability should be correctly dissected and quantified.

Here, we address these points using an electroencephalographic (EEG) dataset collected from a large population of healthy volunteers ($n = 96$). First, we quantitatively compared the two widely used baseline correction approaches (*subtraction* and *percentage*) at three different levels (single-trial, single-subject, and group), and show that the *percentage* procedure, especially when applied at single-trial level, can yield very misleading results, and largely overestimate ERS and underestimate ERD. Since baseline-corrected TFDs are influenced by the trial-to-trial fluctuations in the magnitude of pre-stimulus EEG activity, the *subtraction* approach, albeit unbiased, is not adequate to dissect the trial-to-trial relationships between electrocortical (pre- and post-stimulus EEG activity) and behavioral variables. Thus we characterized the trial-to-trial variability in pre-stimulus EEG power, and explored its influence on the post-stimulus EEG activity and baseline-corrected TFDs. Since ERD/ERS capture the mixed variability of pre- and post-stimulus EEG power, it is difficult to determine whether the trial-to-trial relationship between ERD/ERS and behavior variables is contributed by pre-stimulus activity, post-stimulus activity, or both. Therefore, we propose a multivariate linear regression (MVLR) model solved using the partial least squares (PLS) method to dissect the trial-to-trial relationships between electrocortical (pre- and post-stimulus EEG activity) and behavioral variables (e.g., intensity of perception).

Materials and methods

Experimental design and EEG recording

Subjects

EEG data were collected from 96 healthy volunteers (51 females) aged 21.6 ± 1.7 years (mean ± SD, range = 17–25 years). All subjects gave their written informed consent and were paid for their participation. The local ethics committee approved the procedures.

Nociceptive stimulation

Radiant-heat stimuli were generated by an infrared neodymium yttrium aluminum perovskite (Nd:YAP) laser with a wavelength of 1.34 μm (Electronical Engineering, Italy). At this wavelength, laser pulses activate directly nociceptive terminals in the most superficial skin layers (Baumgartner et al., 2005; Iannetti et al., 2006). Laser pulses were directed on a square area (5 × 5 cm) centered on the dorsum of the left hand, and defined prior to the beginning of the experimental session. A He–Ne laser pointed to the area to be stimulated. The laser beam was transmitted via an optic fiber and its diameter was set at approximately 7 mm (~38 mm^2) by focusing lenses. The pulse duration was 4 ms, and four different energies (E1: 2.5 J; E2: 3 J; E3: 3.5 J; E4: 4 J) of stimulation were used. After each stimulus, the target of the laser beam was shifted by approximately 1 cm in a random direction, to avoid nociceptor fatigue or sensitization.

Experimental design

Prior to the EEG data collection, we delivered a small number of laser pulses with different stimulus energies to familiarize the subjects with the stimulation. During the EEG data collection we delivered ten laser pulses at each of the four stimulus energies (E1–E4), for a total of 40 pulses. The order of stimulus energies was pseudorandomized. The inter-stimulus interval (ISI) varied randomly between 10 and 15 s (rectangular distribution). An auditory tone delivered between 3 and 6 s after the laser stimulation (rectangular distribution) prompted the subjects to rate the intensity of the painful sensation elicited by the laser stimulus, using a visual analog scale ranging from 0 (corresponding to "no pain") to 100 (corresponding to "pain as bad as it could be").

EEG recording

Subjects were seated in a comfortable chair in a silent, temperature-controlled room. They wore protective goggles and were asked to relax their muscles and focus their attention towards the laser stimuli. EEG data were recorded using 64 channels positioned according to the extended 10–20 system (Brain Products GmbH, Munich, Germany; pass band: 0.01–100 Hz; sampling rate: 1000 Hz). The nose was used as the reference channel, and all channel impedances were kept lower than 10 kΩ. To monitor ocular movements and eye blinks, electro-oculographic (EOG) signals were simultaneously recorded from 4 surface electrodes: one pair placed over the upper and lower eyelids, the other pair placed 1 cm lateral to the outer corner of the left and right orbits.

EEG data analysis

EEG data preprocessing

EEG data were processed using EEGLAB (Delorme and Makeig, 2004), an open source toolbox running in the MATLAB environment, and in-house MATLAB functions. Continuous EEG data were band-pass filtered between 1 and 100 Hz. EEG epochs were extracted using a window analysis time of 1500 ms (500 ms pre-stimulus and 1000 ms post-stimulus) and baseline corrected in the time domain using the pre-stimulus interval (−500–0 ms). Trials contaminated by eye-blinks and movements were corrected using an infomax Independent Component Analysis algorithm (runica) (Delorme and Makeig, 2004; Jung et al., 2001; Makeig et al., 1997). In all datasets, these independent

components had a large EOG channel contribution and a frontal scalp distribution.

Note that the baseline correction in the time domain is a necessary step for the subsequent time–frequency analysis, since, by minimizing large amplitude discontinuities between consecutive trials and removing large baseline signal offset of each trial, it ensures that the Independent Component Analysis denoising and the artifact rejection are optimal.

Time–frequency analysis

A TFD of the EEG time course was obtained using a windowed Fourier transform (WFT) with a fixed 250-ms Hanning window. These TFD parameters allow achieving a good tradeoff between time resolution and frequency resolution within the explored range of frequencies (Zhang et al., 2012).

The WFT yielded, for each time course, a complex time–frequency estimate $F(t,f)$ at each point (t,f) of the time–frequency plane, extending from −500 to 1000 ms (in steps of 1 ms) in the time domain, and from 1 to 100 Hz (in steps of 1 Hz) in the frequency domain. The resulting spectrogram, $P(t,f) = |F(t,f)|^2$, represents the signal power as a joint function of time and frequency at each time–frequency point. When applied to across-trial averages of the response in the time domain, the obtained TFDs only contain brain responses phase-locked to stimulus onsets (ERPs). When applied to single-trial EEG responses, the obtained TFDs contained brain responses both phase-locked (ERPs) and non-phase-locked (ERS and ERD) to stimulus onsets.

To distinguish between phase-locked and non-phase-locked EEG responses, we calculated the phase-locking value (PLV; Lachaux et al., 1999), for each subject, as follows:

$$PLV(t,f) = \left| \frac{1}{N} \sum_{n=1}^{N} \frac{F_n(t,f)}{|F_n(t,f)|} \right| \quad (1)$$

where N is the number of trials.

Time–frequency baseline correction methods

In the time–frequency domain, the spectrograms were baseline-corrected (reference interval: −400 to −100 ms relative to stimulus onset) at each frequency f using two methods: *subtraction* and *percentage*. The reference interval was chosen to avoid the adverse influence of spectral estimates biased by windowing post-stimulus activity and padding values. It is important to note that the length of the reference interval may affect the baseline-corrected TFDs. Theoretically, choosing a long reference interval should lead to a more accurate estimation of the true baseline (Kay, 1993). However, a long reference interval also increases the risk of including unexpected artifacts that were not fully removed during preprocessing. An empirical demonstration that the choice of a reference interval ranging from −400 to −100 ms was appropriate is provided in Section 1 of the Supplementary Materials.

In the *subtraction* method, the baseline correction was achieved by subtracting the average of the baseline interval from all time points of each frequency (Iannetti et al., 2008; Pfurtscheller and Lopes da Silva, 1999):

$$P_s(t,f) = P(t,f) - R(f) \quad (2)$$

where $R(f)$ is the averaged power spectral density of the signal within the pre-stimulus baseline interval.

In the *percentage* method, the percent change from baseline was obtained by dividing the baseline-subtracted values of each frequency by the average of the baseline values of that frequency (Schulz et al., 2011; Zhang et al., 2012):

$$P_p(t,f) = [P(t,f) - R(f)]/R(f) \times 100\%. \quad (3)$$

The resulting baseline-corrected TFDs, representing stimulus-elicited changes in oscillatory magnitude relative to the pre-stimulus baseline interval, are expressed in μV^2 for the *subtraction* method (Eq. (2)) and in ER100% for the *percentage* method (Eq. (3)).

Both baseline correction methods (*subtraction* and *percentage*) were applied on the EEG data at three different levels: (1) at *single-trial level* the baseline correction was performed on each single-trial TFD; (2) at *single-subject level* the baseline correction was performed, in each single-subject, on the TFD averaged across all single trials; and (3) at *group level* the baseline correction was performed on the group level averaged TFD.

Next, we performed a point-by-point one-way repeated-measure ANOVA to assess the differences between TFDs that were baseline corrected at single-trial, single-subject, and group levels. To account for multiple comparisons, the significance level (p value) was corrected using a false discovery rate (FDR) procedure (Benjamini and Hochberg, 1995).

We also proved that, using the *percentage* method, the average of single-trial baseline-corrected TFDs (*single-trial level*) is more likely to be larger than the baseline-corrected averaged TFDs (*single-subject level* or *group level*) using mathematical derivation and simulated data (see Section 2 of the Supplementary Materials).

Since we observed that baseline *subtraction* was unbiased (i.e., it yielded identical TFDs regardless of whether it was performed at single-trial, single-subject or group level; see Time–frequency responses after baseline correction section), single-trial baseline *subtraction* was chosen for the subsequent data analysis.

Estimating trial-to-trial variability in pre-stimulus EEG

Both when using the *subtraction* and the *percentage* baseline correction methods, baseline-corrected TFDs were influenced by the trial-to-trial fluctuations in the magnitude of pre-stimulus EEG activity. To characterize this influence, it is imperative to estimate the variability of pre-stimulus EEG activity. Thus, we first calculated, for each trial, the average power within the pre-stimulus interval of each frequency f. We then explored, for each subject, the relationship between the trial-to-trial variability of pre-stimulus power at each frequency f and trial number n, using a multiple nonlinear regression (MnLR), as follows:

$$R(f) = \beta_1(f) \cdot n + \beta_2(f) \cdot n^2 + \beta_3(f)/n + \beta_4(f) \quad (4)$$

where $R(f)$ is the averaged power at frequency f in the pre-stimulus interval, $\beta_1(f)$, $\beta_2(f)$, and $\beta_3(f)$ are the regression coefficients respectively modeling how $R(f)$ varied *linearly*, *quadratically*, and *inversely* with n, and $\beta_4(f)$ is the coefficient modeling the constant part of $R(f)$.

We performed a one-sample t-test to assess whether each estimated coefficient of each frequency ($\beta_1(f)$, $i = 1$–4) was different from zero. To account for multiple comparisons, the significance level (p value) was corrected using an FDR procedure (Benjamini and Hochberg, 1995).

Influence of the pre-stimulus EEG variability on post-stimulus EEG

The pre-stimulus variability in EEG power, quantified by performing the analyses described in the previous paragraph, may significantly affect the post-stimulus EEG activity and the baseline-corrected TFDs. To evaluate the influence of the variability of pre-stimulus EEG power on post-stimulus EEG power, we first calculated the mean power of pre-stimulus EEG activity for each trial and frequency within the reference interval (−400 to −100 ms relative to stimulus onset) prior to any time-frequency baseline correction, and then classified TFDs for each trial and frequency into four categories (grades 1–4 with decreasing pre-stimulus EEG power; each grade has the same number of trials; thus, grades are equivalent to 25% quartiles). Trials in each category were averaged together, thus obtaining four average TFDs at each frequency and for each subject. To evaluate the influence of the variability of pre-stimulus EEG power on the baseline-corrected TFDs, the average TFD of each of the four categories was baseline corrected using the *subtraction* method (as in Eq. (2)). A point-by-point one-way repeated-measures ANOVA was performed to assess the differences between TFDs across subjects obtained from different grades of pre-stimulus EEG

power (grades 1–4), both before and after baseline correction. To account for multiple comparisons, the significance level (p value) was corrected using an FDR procedure (Benjamini and Hochberg, 1995).

MVLR modeling and PLS analysis

Since ERD/ERS was obtained after baseline correction, the estimates captured the mixed variability of pre- and post-stimulus EEG power. Therefore, when the trial-to-trial relationship between ERD/ERS and behavioral variables needs to be investigated, it becomes difficult to determine whether such relationship is contributed by pre-stimulus activity, post-stimulus activity, or both. To address this problem, we propose a multivariate linear regression (MVLR) model solved using the partial least squares (PLS) method to dissect the trial-to-trial relationships between electrocortical (pre- and post-stimulus EEG activity) and behavioral variables (e.g., intensity of perception).

For each EEG trial, the relationship between the explanatory variables $X(t,f)$ (EEG power at the time–frequency point (t,f)) and the possible dependent variables Y (e.g., behavioral responses like the intensity of perception, experimental factors like pre-stimulus EEG features, or any combination of these factors) can be modeled in a MVLR model as follows:

$$Y = \alpha_0 + \sum_{t,f} \alpha_{t,f} X(t,f) + \varepsilon \quad (5)$$

where $\alpha_{t,f}$ is the model coefficient of the EEG power at each time–frequency point, α_o is the intercept, and ε is the model residual.

Because (i) the number of explanatory variables $X(t,f)$ was markedly larger than the number of observations (EEG trials), and (ii) there could be strong collinearity among EEG activity at nearby time–frequency points, as well as among the dependent variables, the ordinary least-squares estimation is not appropriate to solve the above MVLR model. PLS regression is an efficient method to overcome the above-mentioned problems, as it extracts the maximal covariance between the explanatory variables and the dependent variables by a small number of uncorrelated latent components (Abdi and Williams, 2013). Here, these latent components were estimated using the Nonlinear Iterative Partial Least Squares algorithm (NIPALS; Wold et al., 2001). The number of latent components in the PLS analysis was estimated using the coefficient of determination (Steel et al., 1997), which calculates the percentage of the variance of the values fitted by the latent components and the total variance of the dependent variables.

In PLS analysis, both MVLR model coefficients and the Variable Importance on Projection (VIP) should be used as indexes to select important explanatory variables (Wold, 1995). The model coefficients represent the importance of each explanatory variable in the prediction of the dependent variables, while the VIP values show the contribution of each explanatory variable to modeling both the dependent and the explanatory variables. Therefore, along with the model coefficients, VIP values were calculated to explore the time–frequency features that were important to explain the dependent variables.

To test whether the PLS performance was influenced by baseline correction or by including a new dependent variable into the MVLR model, we performed four parallel PLS regression analyses using different explanatory and dependent variables. The explanatory variables were either (1) TFDs of EEG activity without baseline correction ($P(t,f)$) or (2) TFDs of EEG activity with baseline *subtraction* ($P_s(t,f)$). The dependent variables were either (1) subjective intensity of perception or (2) both intensity of perception and pre-stimulus α-power. The pre-stimulus α-power is calculated as the mean value within the pre-stimulus interval (−400 to −100 ms) at α frequencies (8–12 Hz) for each trial, and it is chosen as an additional dependent variable for the purposes of (1) illustrating how baseline correction influences the inference of the relationship between explanatory and dependent variables if the variability of dependent variable is largely determined by pre-stimulus EEG power, and (2) validating the correctness and robustness of PLS analysis even if a new dependent variable is included in the MVLR model.

After the model coefficients $\alpha_{t,f}$ of the four MVLR models were estimated, we performed a point-by-point two-way repeated-measures ANOVA on the model coefficients explaining the intensity of perception, to assess the effects of the factors 'baseline correction' (two levels: $P(t,f)$ vs. $P_s(t,f)$), and 'inclusion of a new dependent variable' (two levels: with pre-stimulus α-power vs. without pre-stimulus α-power). To account for multiple comparisons, the significance level (p value) was corrected using an FDR procedure (Benjamini and Hochberg, 1995).

To test whether the model coefficients $\alpha_{t,f}$ and VIP values within the post-stimulus interval were significantly different from those within the pre-stimulus interval, we performed a bootstrapping test (Delorme and Makeig, 2004; Durka et al., 2004; Hu et al., 2012). At each time–frequency point (t. f), we extracted a collection of numerical samples from the 96 subjects, and compared with a similar collection of numerical samples in the baseline interval. The null hypothesis was that there was no difference between the means of the two numerical samples, i.e., no difference between the mean amplitude values within pre-stimulus and post-stimulus intervals. The pseudo-t statistic of two populations was calculated, and its probability distribution was estimated by permutation testing (5000 times). The distribution of the pseudo-t statistics from the baseline population was obtained, and the bootstrap p values for the null hypothesis were generated. This procedure identified the time–frequency regions in which the modeled coefficients and VIP values were significantly different relative to the baseline interval (Hu et al., 2012; Peng et al., 2012). To account for multiple comparisons, the significance level (expressed as p value) was corrected using an FDR procedure (Benjamini and Hochberg, 1995). Importantly, since model coefficients and VIP values provide complementary information to select important explanatory variables (Chong and Jun, 2005), it is recommended to combine model coefficients and VIP in the PLS analysis to achieve an optimal explanatory variable selection (Chong and Jun, 2005; Wold, 1995). Thus, we extracted the intersection of the significant time–frequency regions, in which both model coefficients and VIP values were significantly different relative to the baseline interval.

Results

Time–frequency responses without baseline correction

Fig. 1 shows the EEG responses elicited by laser stimulation in 96 subjects, at electrode C4 (contralateral to the stimulation side). The top left panel shows the response in the time domain, characterized by the large N2–P2 biphasic complex (LEPs). Single-subject average waveforms (color-coded) are superimposed. The black waveform represents the group level average. The top right panel shows the group-level average of the TFDs obtained from the single-subject average LEPs. This TFD contains a clear response located at 100–400 ms and 1–10 Hz. This time–frequency response ('LEP') corresponds to the N2–P2 biphasic complex of LEPs in the time domain (Fig. 1, top left panel). The bottom left panel shows the group-level PLVs, indicating that only the 'LEP' responses were phase-locked to the stimulus onset, while other TFD responses were not phase-locked to stimulus onset and thus cannot be detected after single trials are averaged in the time domain. The bottom right panel shows the group-level average of the TFDs obtained from single-trial LEPs, containing both the large 'LEP' response and a more subtle increase of power in the γ range, located at 100–300 ms and 60–80 Hz (Fig. 1).

Time–frequency responses after baseline correction

Fig. 2 B1–B3 shows the time–frequency responses after baseline *subtraction* (Eq. (2)), which revealed that laser stimuli elicited not only the large phase-locked response ('LEP': 100–400 ms, 1–10 Hz), but also two non-phase-locked responses, consisting of (1) a transient increase

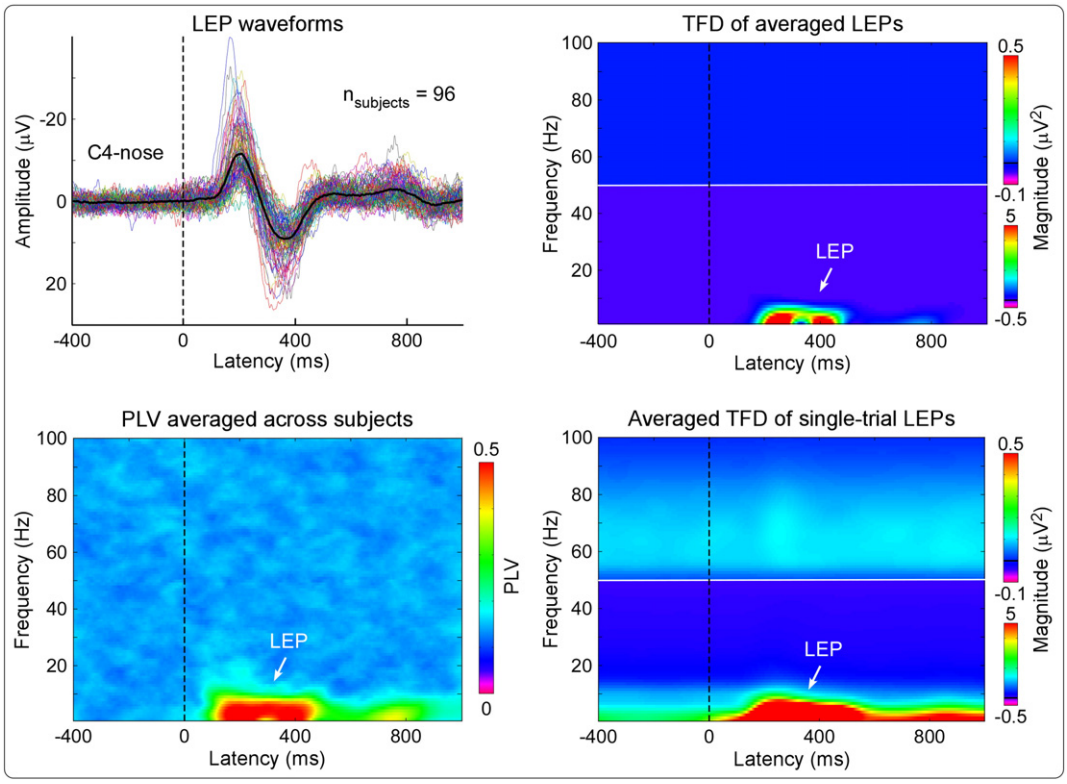

Fig. 1. Laser-elicited EEG responses. Displayed signals were recorded from 96 subjects at electrode C4 (nose reference). *Top left:* Time domain LEP waveforms. Single-subject average waveforms are color-coded and superimposed, and the group average waveform is marked with black thick line. *Top right:* Group-level average of the TFDs obtained from single-subject average LEPs, containing a clear response ('LEP') located at 100–400 ms and 1–10 Hz. *Bottom left:* Group-level average of phase-locking value obtained from single-trial LEPs, showing a large value at 'LEP' region. *Bottom right:* Group-level average of the TFDs obtained from single-trial LEPs, containing both the large 'LEP' response, and a very subtle increase of power in the γ range, located at 100–300 ms and 60–80 Hz.

of power in the γ band ('γ-ERS': 100–300 ms, 60–80 Hz) and (2) a long-lasting decrease of power in the α band ('α-ERD': 400–900 ms, 8–12 Hz) (Fig. 2 B1–B3).

Crucially, these results were identical regardless of whether baseline *subtraction* (Fig. 2 B1–B3) was performed at single-trial, single-subject or group level ($p = 1$, FDR-corrected; Fig. 2 D1). In contrast, when baseline correction was performed using the *percentage* method (Eq. (3)), the results were dramatically different at single-trial, single-subject, and group levels (Fig. 2 C1–C3) ($p < 0.05$, FDR-corrected; Fig. 2 D2). When the baseline *percentage* was computed at group level, the obtained time–frequency responses (i.e., 'LEP', 'γ-ERS', and 'α-ERD') are highly similar to those identified using the *subtraction* method. However, when the baseline *percentage* was computed at single-trial level, there was a significantly stronger 'γ-ERS' (100–300 ms, 60–100 Hz), together with a strong and diffuse increase of power for all frequencies during the post-stimulus interval (0–900 ms, 1–100 Hz).

This large increase of post-stimulus power observed in single-trial vs. group level baseline *percentage* approaches was significant ($p < 0.05$, FDR-corrected). Importantly, this increase was not determined by the stimulus, but reflected a bias introduced by the baseline *percentage* approach performed at single-trial level. Another practical consequence of this bias is the disappearance of the 'α-ERD' (400–900 ms, 8–12 Hz) (Fig. 2 C1). Thus, baseline correction performed using *percentage* introduces a general overestimation of post-stimulus oscillation magnitudes. In other words, the *percentage* approach overestimates the stimulus-induced power increase (ERS), and underestimates the stimulus-induced power decrease (ERD). A detailed mathematical demonstration of the positive bias determined by the single-trial baseline *percentage* approach, together with an analysis performed using simulated data is provided in Section 2 of the Supplementary Materials.

While the maximal positive bias was determined by baseline correcting the TFDs using the *percentage* approach at single-trial level, a smaller, but nevertheless significant positive bias was also introduced when the baseline correction was performed using the *percentage* approach at single-subject level ($p < 0.05$, single subject vs. group level post-hoc comparison, FDR-corrected).

Variability in pre-stimulus EEG activity

We examined the trial-to-trial variability of the pre-stimulus EEG power using the MnLR model of Eq. (4). We found a significant across-trial variability of pre-stimulus power, which followed a hyperbolic function of the trial order n (modeled by the regressor $1/n$, in blue in Fig. 3). This variability was significant in several frequency bands, although in different directions (negative in 7–15 Hz; positive in 32–35 Hz, 62–65 Hz, and 90–92 Hz; $p < 0.05$, one sample t test and FDR-corrected) (Fig. 3, top panel). In other words, the pre-stimulus EEG power rapidly increased (or decreased) in the first few trials, and then changed more slowly in the following trials. To intuitively demonstrate this variability, we displayed the magnitude of the pre-stimulus α-power (8–12 Hz) throughout all single trials, across all subjects (Fig. 3, bottom panel). Such pre-stimulus α-power showed a significantly negative modulation modeled by the regressor $1/n$, and the fitted curve obtained from MnLR displayed a large increase in the first few trials, followed by a smaller increase in the subsequent trials.

After baseline correction, the pre-stimulus EEG variability affects the post-stimulus EEG

Without baseline correction, the variability in pre-stimulus EEG power (modeled as four grades) did not affect the post-stimulus EEG power ($p > 0.05$, one-way repeated-measures ANOVA, FDR-corrected), except in some high-frequency regions (e.g., around 400 ms and 90 Hz) (Fig. 4, top panel). After baseline correction using the *subtraction*

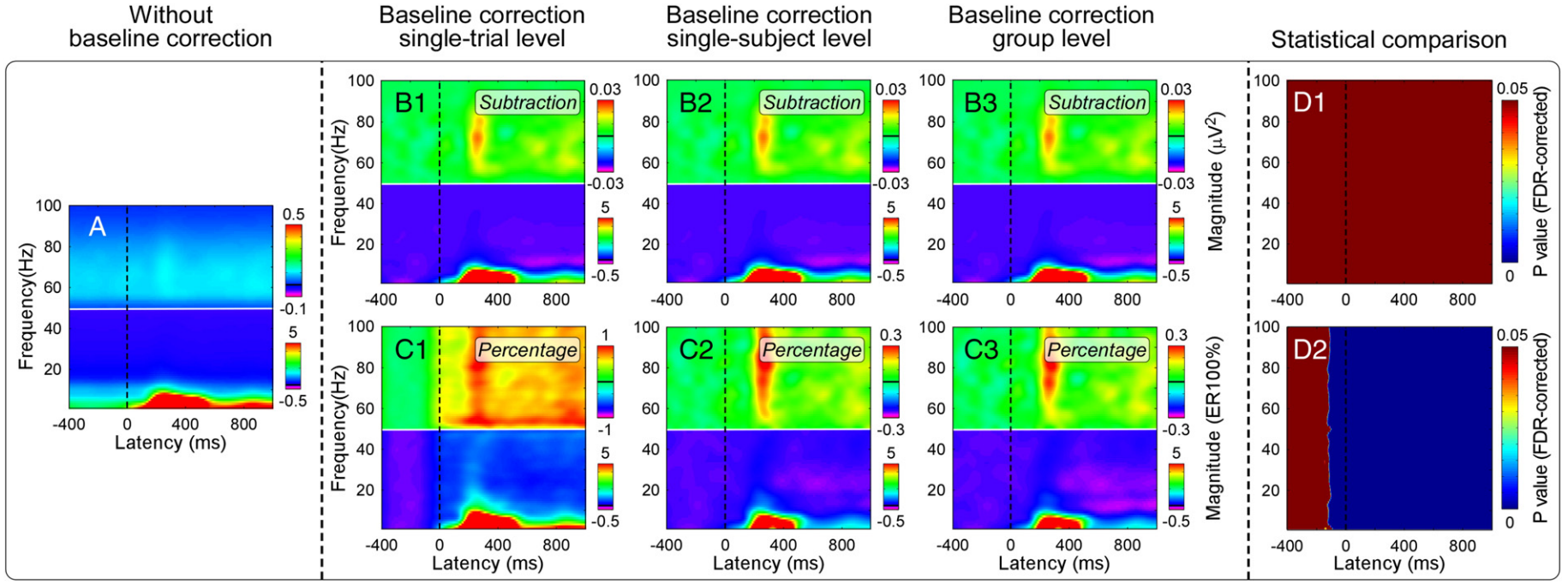

Fig. 2. The performance of different baseline correction strategies. *Left:* Group-level average of the TFDs obtained from single-trial LEPs without baseline correction (expressed in μV^2). *Middle*: Group-level average of the TFDs after baseline *subtraction* (B1–B3) and *percentage* (C1–C3) at single-trial (B1, C1), single-subject (B2, C2) and group levels (B3, C3). The color scale represents the average decrease (ERD) or increase (ERS) of oscillation power (expressed in μV^2 for *subtraction* and in ER100% for *percentage*), relative to the pre-stimulus baseline interval (−400 to −100 ms). *Right:* One-way repeated-measures ANOVA to assess the effect of baseline correction level (single-trial, single-subject, and group) on the TFDs of stimulus-elicited EEG responses. The color scale represents the statistic p value (FDR-corrected). Time–frequency regions with significant differences in the TFDs baseline-corrected at single-trial, single-subject, and group levels are marked in blue. Non-significant regions are marked in brown.

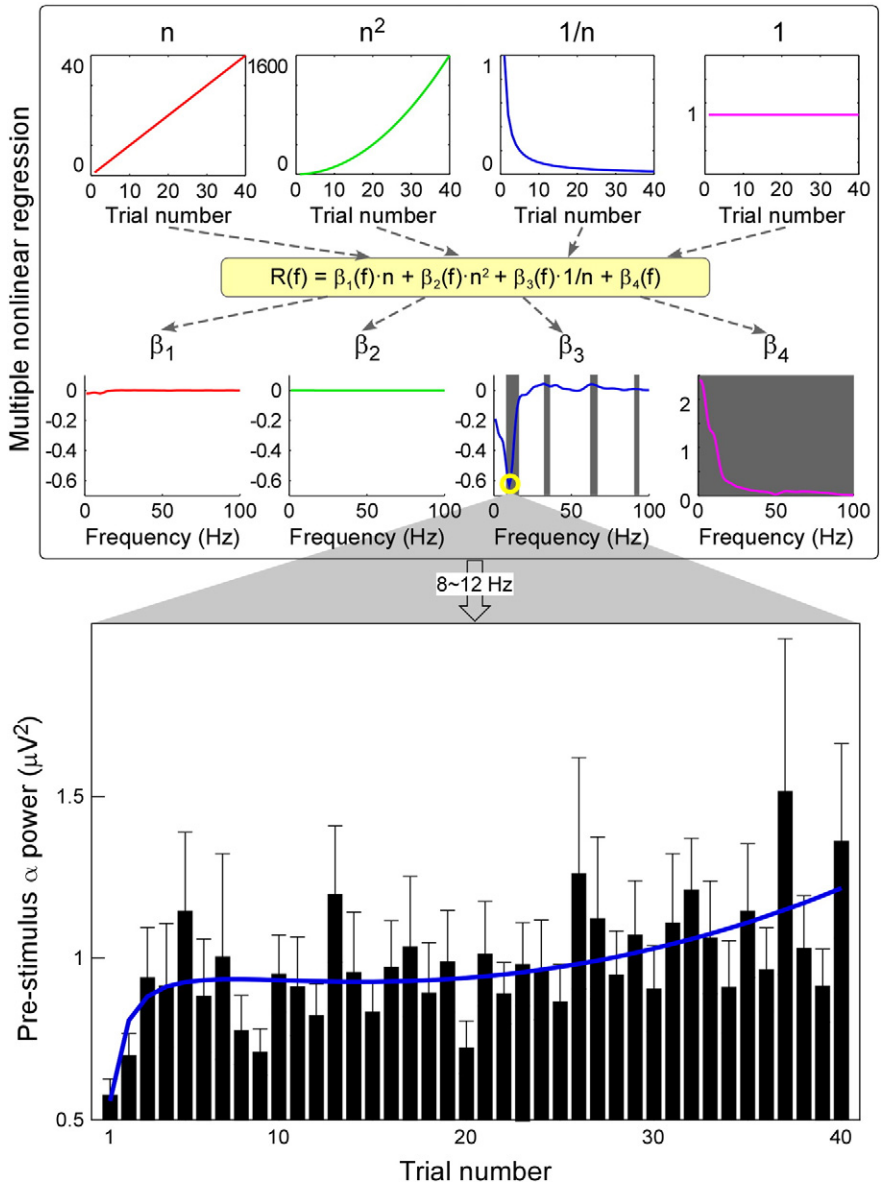

Fig. 3. Variability in pre-stimulus EEG activity. *Top:* The pre-stimulus EEG power was modeled using an MnLR model (*middle*). Four regressors (n, n^2, $1/n$, 1; *top*) were used to model the variability of pre-stimulus EEG power for each subject. The resulting coefficients (β values) for each frequency of each regressor were displayed in the *bottom* of this panel. Frequency intervals, in which the obtained β values were significantly different from zero, were marked in gray ($p < 0.05$, one sample t test and FDR-corrected). *Bottom:* The pre-stimulus α-power (8–12 Hz) showed a significantly negative modulation modeled by the regressor $1/n$ (marked with a yellow circle), which indicated a large initial increase, followed by a smaller increase in the subsequent trials. Black bars represent the mean of pre-stimulus α-power across subjects for each trial (expressed as mean ± SEM). Blue solid line represents the curve fitted to pre-stimulus α-power obtained from multiple nonlinear regression.

approach, however, the variability in pre-stimulus EEG power was dramatically reflected in most post-stimulus time–frequency regions ($p < 0.05$, one-way repeated-measures ANOVA, FDR-corrected), with the sole exception of the low frequency phase-locked response ('LEP') (Fig. 4, bottom panel). Therefore, a significant part of the trial-to-trial variability ascribed to ERD/ERS after baseline correction was not determined by the stimulus, but instead consequent to the variability of the pre-stimulus power.

MVLR model and PLS analysis

We used PLS analysis to dissect the contribution of pre- and post-stimulus EEG variability on the trial-to-trial relationship between ERD/ERS and dependent variables. We ran four parallel MVLR models and PLS analyses to explain either one dependent variable (intensity of perception) or two dependent variables (intensity of perception and pre-stimulus α-power) using TFDs of EEG activity with and without baseline correction. Model coefficients explaining the intensity of perception were virtually identical, regardless of whether the preliminary baseline correction was performed, or whether the α-power was included as an additional dependent variable ($p > 0.05$, two-way repeated-measures ANOVA, FDR-corrected; Fig. 5). This finding indicates that the dependent variable ('intensity of perception') was largely reflected by post-stimulus EEG variability. As expected, model coefficients explaining the pre-stimulus α-power were strong and positive in the pre-stimulus region (−400 to −100 ms, 8–12 Hz) when TFDs of EEG activity without baseline correction $P(t,f)$ were used as the explanatory variables, but strong and negative in the post-stimulus region (0–1000 ms, 8–12 Hz) only when baseline-corrected TFDs ($P_s(t,f)$) were used as the explanatory variables (Fig. 5).

Since both baseline correction and inclusion of a new dependent variable did not affect the estimation of model coefficients explaining the

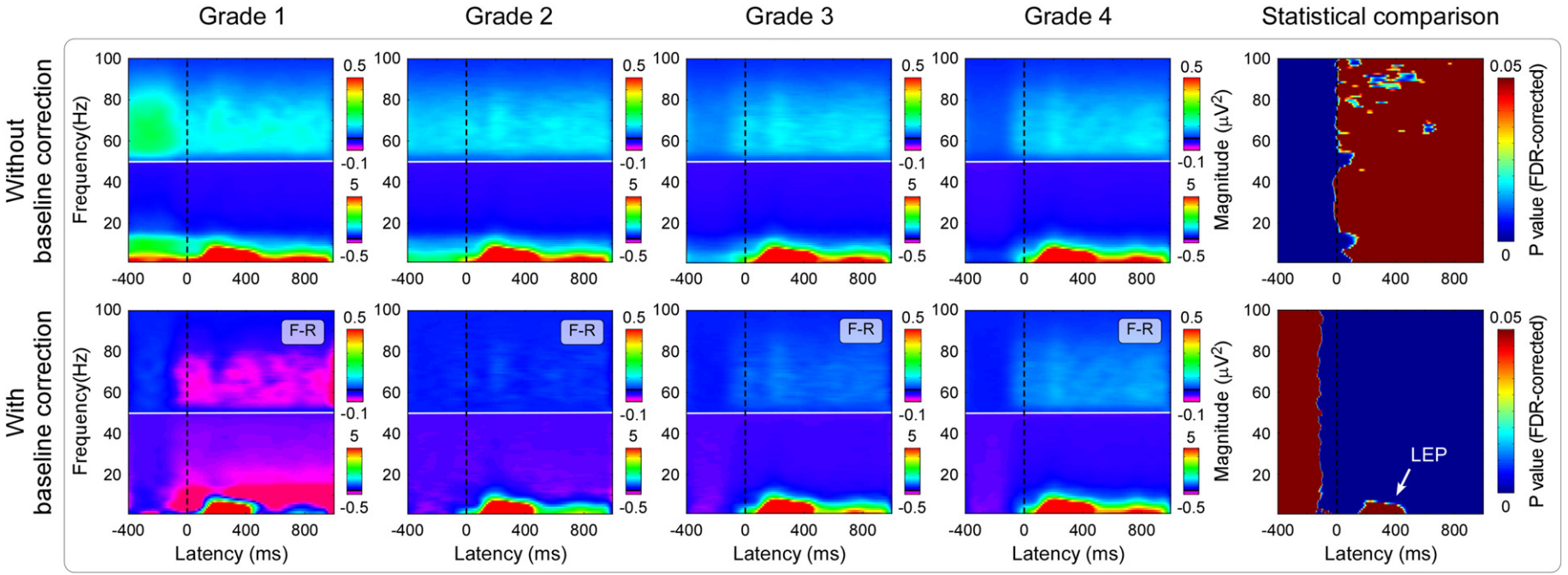

Fig. 4. Influence of pre-stimulus EEG variability on post-stimulus EEG variability with and without baseline correction using the *subtraction* method. *Top left:* Without baseline correction, TFDs of laser-elicited EEG responses at different grades of pre-stimulus EEG power for each frequency (Grade 1: the highest pre-stimulus EEG power for each frequency; Grade 4: the lowest pre-stimulus EEG power for each frequency; and Grades 2 and 3 in between). *Top right:* Without baseline correction, the variability in pre-stimulus EEG power did not affect the post-stimulus EEG power except in some high-frequency regions (e.g., around 400 ms in latency and 90 Hz in frequency). The color scale represents the statistic p value (FDR-corrected). For each of the different grades of pre-stimulus EEG power, time–frequency regions with significant differences in the TFDs are marked in blue, while non-significant regions are marked in brown. *Bottom left:* The TFDs of each grade were baseline corrected using the *subtraction* approach. *Bottom right:* With baseline correction, the variability of pre-stimulus EEG power was mainly reflected in most post-stimulus time–frequency regions, except the low-frequency phase-locked response ('LEP').

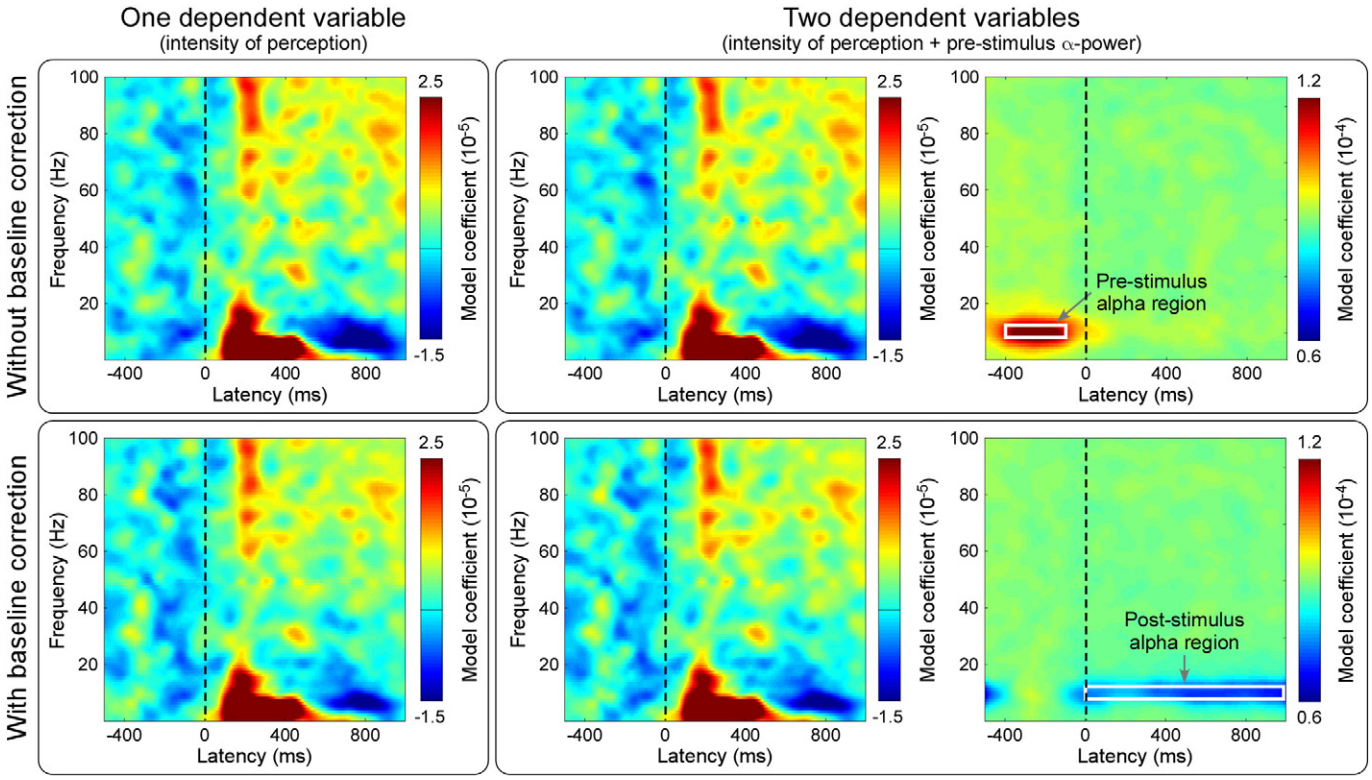

Fig. 5. Partial least squares (PLS) analysis to assess the relationship between EEG activity and behavioral variables. PLS analysis was performed on TFDs of LEP responses with and without baseline correction (*top* and *bottom* panels respectively) to explain one dependent variable (intensity of perception; *left*) and two dependent variables (intensity of perception and pre-stimulus α-power; *right*). Both baseline correction and inclusion of a new dependent variable did not affect the estimation of model coefficients explaining the intensity of perception ($p > 0.05$, two-way repeated-measures ANOVA, FDR-corrected). In contrast, model coefficients explaining the pre-stimulus α-power were strongly affected by baseline correction, showing a positive value at the pre-stimulus region (−400 to −100 ms, 8–12 Hz) without baseline correction and a negative value at the post-stimulus region (0–1000 ms, 8–12 Hz) with baseline correction.

intensity of perception, a representative performance of PLS analysis was illustrated when TFDs of EEG activity without baseline correction were used as the explanatory variables and intensity of perception was used as dependent variable (Fig. 6). In this case, the coefficient of determination, expressing the percentage of the variance of the values fitted by the latent components and the total variance of the dependent variables, was 75 ± 12% across subjects. This observation indicates that the extracted latent component could explain the greater part of the variance of the dependent variable. The calculated model coefficients and VIP values showed that the fitting of the PLS model was commonly contributed by three distinct time–frequency regions ('LEP': 100–400 ms, 1–20 Hz; 'α-ERD': 600–900 ms, 6–13 Hz; and 'γ-ERS': 150–350 ms, 60–100 Hz) (Fig. 6). The summarized VIP values were 1.46 ± 0.30, 0.94 ± 0.28, and 0.89 ± 0.29 for 'LEP', 'α-ERD', and 'γ-ERS', respectively. In addition, the model coefficients of power spectral density, $P(t,f)$, revealed that the single-trial magnitude of 'LEP' and 'γ-ERS' (summarized coefficients were $[3.1 \pm 1.4] \times 10^{-5}$ and $[1.1 \pm 1.4] \times 10^{-5}$ respectively) was positively modulated by the intensity of perception, while

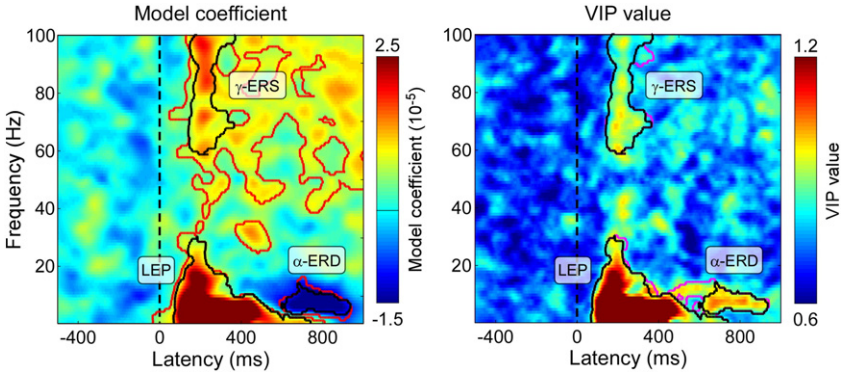

Fig. 6. Partial least squares (PLS) analysis and the statistical determination of significant time–frequency regions. PLS analysis was performed on TFDs of laser-elicited EEG activity without baseline correction to explain the intensity of perception. As compared to the pre-stimulus interval, significant differences of model coefficients, VIP values, and their intersection are outlined in red, pink, and black respectively. Model coefficients and VIP values jointly showed that the determination of PLS model was mainly contributed by 'LEP' (100–400 ms, 1–20 Hz), 'α-ERD' (600–900 ms, 6–13 Hz), and 'γ-ERS' (150–350 ms, 60–100 Hz). In addition, model coefficients revealed that EEG powers of 'LEP' and 'γ-ERS' were positively modulated by the intensity of perception, while EEG power of 'α-ERD' was negatively modulated by the intensity of perception ($p < 0.05$, FDR-corrected).

the single-trial magnitude of 'α-ERD' (summarized coefficients were $[-1.3 \pm 1.8] \times 10^{-5}$) was negatively modulated by the intensity of perception ($p < 0.05$, FDR-corrected).

Discussion

The present study yielded four main findings. First, performing the baseline correction using the *percentage* approach introduces a positive bias in the estimation of TFDs, resulting in ERD underestimation and ERS overestimation. In contrast, no bias is introduced when the baseline correction is performed using the *subtraction* approach. Second, the pre-stimulus EEG power (especially in the α band) varies significantly from trial to trial, following a hyperbolic function of the trial order. Third, the variability of ERD and ERS is not only determined by the stimulus, but is also greatly influenced by the trial-by-trial variability of pre-stimulus EEG power. Fourth, MVLR model and PLS analysis allow dissecting the contribution of both pre-stimulus and post-stimulus variability to the trial-to-trial relationship between EEG activity and behavioral variables, such as intensity of perception. In summary, combining single-trial baseline *subtraction* approach with PLS regression allows achieving a correct detection and comprehensive understanding of the functional significance of stimulus-induced ERD/ERS.

Single-trial baseline correction of time–frequency representation

TFDs were identical regardless of whether the baseline *subtraction* was performed at single-trial, single-subject, or group level (Fig. 2 B1–B2), whereas TFDs obtained by baseline *percentage* at single-trial, single-subject or group level were dramatically different (Fig. 2 C1–C3). The baseline *percentage* introduced a strong positive bias of TFD magnitudes at single-trial level (Fig. 2 D2), which lead to the disappearance of the 'α-ERD' (400–900 ms, 8–12 Hz) at single-trial level (Fig. 2 C1), and to its reduction at single-subject level (Fig. 2 C2). In the field of pain electrophysiology, this bias explains why the laser-induced 'α-ERD' is normally reported when ERD/ERS are expressed using the baseline *percentage* approach performed at single-subject level (Iannetti et al., 2008; Mouraux et al., 2003; Ohara et al., 2004; Ploner et al., 2006), but not when it is performed at single-trial level (Schulz et al., 2012b; Zhang et al., 2012).

Given that the baseline *percentage* approach, despite having been used in a large number of studies (Iannetti et al., 2008; Mouraux et al., 2003; Ohara et al., 2004; Ploner et al., 2006; Schulz et al., 2012b; Zhang et al., 2012), introduces a significant bias in the estimate of time–frequency EEG responses, it is necessary that forthcoming studies use the baseline *subtraction* approach, to avoid underestimating ERD and overestimating ERS. It is important to highlight that the magnitude of stimulus-induced changes in low frequencies (<10 Hz) are normally several orders higher than those in high frequencies (>40 Hz). Thus, it is recommended that TFDs obtained by baseline *subtraction* approach are displayed using different scales for low and high frequencies (e.g., Fig. 2).

Variability in pre-stimulus EEG activity and its influence on ERS/ERD

The magnitude of pre-stimulus EEG power of the present dataset significantly varied across trials in several frequency bands (7–15 Hz, 32–35 Hz, 62–65 Hz, and 90–92 Hz; Fig. 3, top panel). This variability followed a hyperbolic function of the trial order, with a rapid change across the first few trials, and a slower, steady change in the remaining trials (e.g., Fig. 3, bottom panel). Such variability of pre-stimulus EEG power did not affect the post-stimulus EEG power without baseline correction, except in some high-frequency regions (e.g., around 400 ms and 90 Hz) (Fig. 4, top panel). However, after baseline correction using the *subtraction* approach, the variability of pre-stimulus EEG power was dramatically reflected in a large number of post-stimulus time–frequency regions, except the low-frequency phase-locked response corresponding to the vertex ERP in the time domain ('LEP') (Fig. 4, bottom panel). Therefore, after baseline correction, the trial-to-trial variability of ERD/ERS is not only determined by the stimulus, but heavily affected by the pre-stimulus variability (Hu et al., 2013). In particular, as demonstrated in Eqs. (2)and (3), the ERD variance was largely influenced by the variability of pre-stimulus EEG power, while the ERS variance was largely influenced by the variability of post-stimulus EEG power (Hu et al., 2013).

Thus, the trial-to-trial variability of ERD/ERS reflects the combination of pre- and post-stimulus EEG variability. In other word, changes of ERD/ERS could reflect mixed variability of changes in the state of the system (reflected in pre-stimulus EEG power) (Del Percio et al., 2006; Hu et al., 2013; Laufs et al., 2003) and changes induced by the stimulus or task (reflected in post-stimulus EEG power) (Peng et al., 2012; Ploner et al., 2006; Stancak et al., 2003). To dissect the contributions of such different physiological determinants of ERD/ERS, it is mandatory to estimate reliably the variability of both pre- and post-stimulus EEG power (Hu et al., 2013). Unfortunately, even performing an unbiased baseline correction (i.e., using the *subtraction* approach), it is not sufficient to isolate the contribution of pre- and post-stimulus EEG to the trial-to-trial ERD/ERS variability, especially when the pre-stimulus EEG variability is evident and physiologically or psychologically relevant.

MVLR modeling and PLS analysis: beyond single-trial baseline correction

The fact that any single-trial baseline correction approach mixes the variability of both pre- and post-stimulus EEG power makes the interpretation of the trial-to-trial relationship between ERD/ERS and behavioral/experimental variables inappropriate. The MVLR modeling and PLS analysis allow solving this problem, by modeling simultaneously pre- and post-stimulus EEG power, and thus calculating their respective contributions to ERD/ERS. Since the PLS analysis identifies the maximal covariance between explanatory variables (e.g., EEG power) and dependent variables (e.g., the intensity of perception) using a small number of uncorrelated latent components (Abdi and Williams, 2013), it has two important advantages compared to traditional mass-univariate analyses (Wold et al., 2001). First, PLS works effectively when the number of explanatory variables is larger than the number of observations (for example, in the present study, we estimated 100 × 1500 model coefficients using 40 trials only). Second, PLS works effectively even when there is strong collinearity among the explanatory variables or dependent variables (for example, in the present study, the strong correlation between power spectral density of nearby time–frequency points). Because of such advantages, PLS analysis allows better exploration of the relationships between TFDs of EEG responses and behavioral variables (e.g., intensity of perception). Furthermore, the differential contribution of the variability in pre- and post-stimulus EEG power in determining the behavioral variable is reflected in the estimated model coefficients (e.g., Fig. 5).

In the present study, the four parallel MVLR models (explaining either one dependent variable [intensity of perception] or two dependent variables [intensity of perception and pre-stimulus α-power] using TFDs of EEG activity with and without baseline correction) showed (1) that similar model coefficients explained the intensity of perception, regardless of baseline correction and inclusion of pre-stimulus α-power as dependent variable; and (2) that different model coefficients explained the pre-stimulus α-power with and without baseline correction (Fig. 5). The first observation indicates that the variability of the dependent variable is largely explained by variability in post-stimulus EEG power when the relationship between explanatory and dependent variable is similar with and without baseline correction. The second observation indicates that the variability of the dependent variable is largely determined by variability in pre-stimulus EEG power when the relationship between explanatory and dependent variable is different with and without baseline correction. Therefore, a statistical comparison between the model coefficients estimated before and after baseline

correction can differentiate time–frequency EEG features that are dominantly determined by the variability of either pre- or post-stimulus EEG power. For example, the PLS estimation of the model coefficients explaining the intensity of perception, which is largely determined by the variability of post-stimulus EEG power, was not affected by the inclusion of pre-stimulus α-power as an additional dependent variable (Fig. 5).

By exploiting the power of PLS analysis, we achieved a comprehensive estimate of the relationship between laser-induced EEG responses and perceived pain intensity. Subjective intensity of perception was reflected in the increase of two TFD ROIs ('LEP': 100–400 ms, 1–20 Hz and 'γ-ERS': 150–350 ms, 60–100 Hz) and in the decrease of one TFD ROI ('α-ERD': 600–900 ms, 6–13 Hz) (Fig. 6). Also, we ascertained that post-stimulus EEG power, and not pre-stimulus EEG power, significantly relates to the intensity of perception. This is important, as there are several inconsistencies in previous report from different research groups (Babiloni et al., 2006; Gross et al., 2007; Mouraux et al., 2003; Schulz et al., 2011, 2012a; Zhang et al., 2012).

Conclusions

Here we show that performing a baseline correction of single-trial TFDs of EEG power using the *percentage* approach introduces a bias in the subsequent estimation of ERD/ERS. In contrast, the baseline *subtraction* approach is unbiased, and allows minimizing the dominance of low-frequency EEG power, thus making the magnitudes of ERD and ERS comparable between low and high frequencies, and highlighting subtle stimulus-elicited changes of oscillatory power. However, although unbiased, the baseline *subtraction* approach unavoidably mixes the variance of pre- and post-stimulus powers. A PLS regression analysis that includes both pre- and post-stimulus powers in an MVLR model, allows reliable estimation of the respective contribution of pre- and post-stimulus powers to the trial-to-trial relationships between ERD/ERS and behavioral variables. Thus, the combination of single-trial baseline *subtraction* approach and PLS regression allows a full exploration of stimulus-induced electrocortical oscillations in a wide range of neuroscientific applications.

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Conflict of interest statement

The authors declare no competing financial interests.

Appendix A. Supplementary Materials

Supplementary Materials to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.09.055.

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