ReSync: Correcting the trial-to-trial asynchrony of event-related brain potentials to improve neural response representation

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Abstract: For various reasons, the brain response activities in EEG signals are not perfectly synchronized from trial to trial with respect to event markers – a problem commonly referred to as ERP latency jitter. EEG experimental technologies have been greatly advanced to reduce technical timing errors so as to reduce the jitter. However, there are intrinsic sources of jitter that are difficult, if not impossible, to remove. The problem becomes more complicated when facing multiple sub-components with different jitter. The jitter issue renders trial-averaged ERP inaccurate at best and misleading at worst. Effectively correcting the jitter has profound significance in brain research. I present a simple method and easy-to-use toolbox ReSync for correcting ERP jitters based on signal processing theories and techniques. ReSync can be used to correct multiple overlapping ERP sub-components with different degrees of jitter without affecting each other (including the static one). The theories, principles, technical details, and limitations of ReSync were presented in this paper, along with a series of simulation and real data examples for evaluating and validating the method.

Keywords: Event-related potential; Brain response variability; ERP latency jitter correction; single trial ERPs; ERP decomposition

1. Introduction

1.1 The Importance of Timing Precision in Brain Response Characterization by ERP

Characterization of dynamic brain response to stimuli in cognitive tasks forms a cornerstone in neurocognitive research. To understand how dynamic cognitive processes unfold in the brain, neuroscientists usually give the brain a 'kick' (sensory input) and observe its dynamic neural response, like physicists studying the motions of a pendulum and its governing laws (Fig 1a, b). EEG technology provides a non-invasive means to observe such dynamic neural responses with millisecond resolution. As EEG signal contains a large amount of spontaneous activity, the pattern of the response activity to the 'kick', i.e., ERP, becomes visible only after averaging multiple trials (Fig 1c). Such a trial-averaged ERP approach provides a great venue for studying brain responses and has given birth to fruitful research outcomes in cognitive research over the last century.

However, the average ERP has long been recognized to be subject to the latency jitter issue – the single trial activation components may not be locked to the event marker with a fixed latency from trial to trial, rendering the average ERP a blurred representation of the neural response (Fig 1c, d). This variability may stem from neural functional mechanisms (e.g., adaptation and learning (Brooks, Carriot, & Cullen, 2015; Cavanagh & Frank, 2014; A. G. E. Collins & M. J. Frank, 2018; Dhawale, Smith, & Olveczky, 2017)), from dynamical nature of multilevel neural working (Mendonca et al., 2016), or simply from noise (Faisal, Selen, & Wolpert, 2008) or technical issues (Peirce et al., 2019). And furthermore, at neural cognitive level, different ERP sub-components may display different degrees or features of jitter. The latency jitter issue may mislead interpretations of neural mechanisms in neurocognitive research (Stokes & Spaak, 2016).

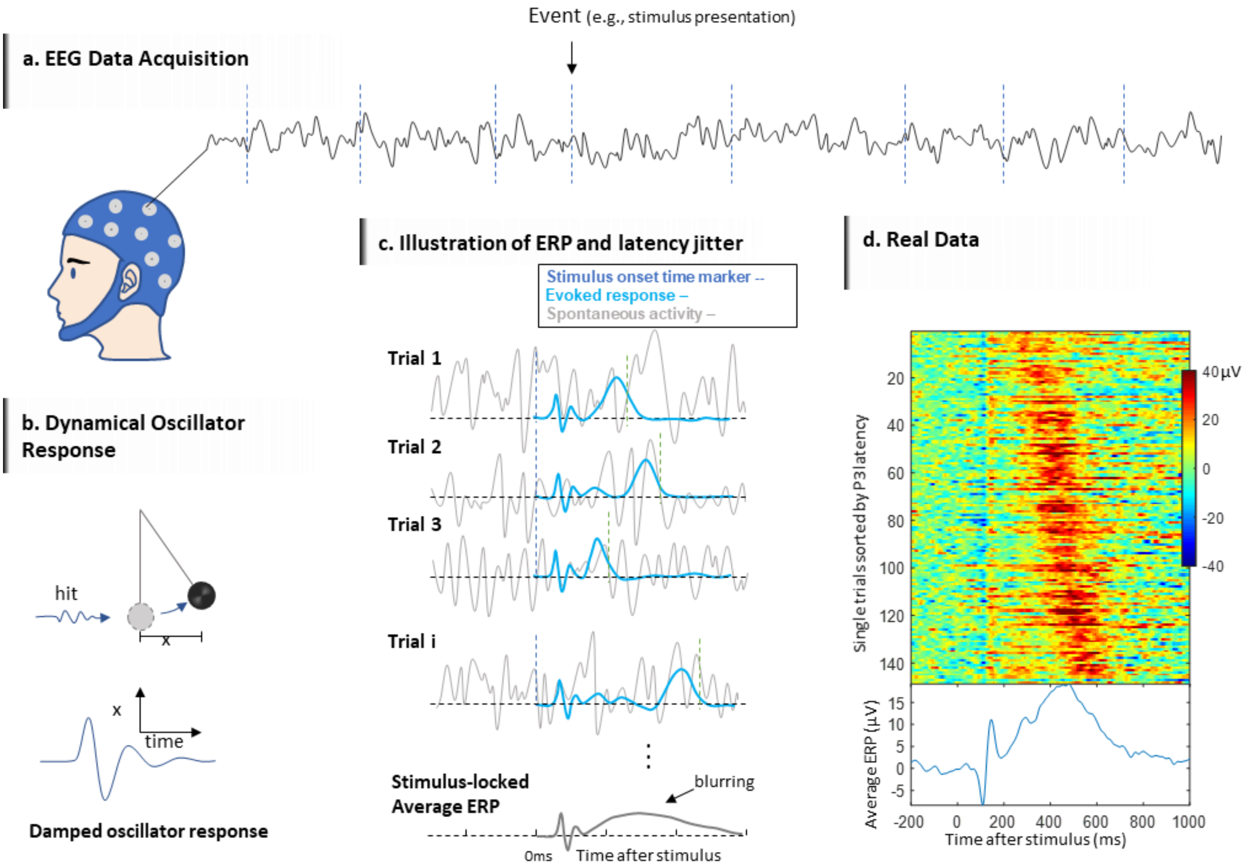

Figure 1. EEG as a tool to characterize dynamic brain response. (a) A typical EEG experiment paradigm in which discrete events are presented to the subject to elicit brain response while continuous EEG signal is being recorded. (b) Eliciting brain response by stimulus can be analogized to hitting a pendulum and observing its dynamic response. (c) The average ERP method assumes that a specific response activity is evoked by stimulus and is added to the spontaneous activity (This is based on additive model. An alternative model, phase resetting model, assumes that ERP is generated by phase resetting of spontaneous activity, see (Sauseng et al., 2007)). By averaging a number of trials to stimulus onsets the spontaneous activity will be cancelled out and the evoked response will remain. However, due to the trial-to-trial variability of brain response, the average ERP may end up showing a blurred version of the response pattern. (d) Real EEG data showing that there are different sub-components in the single trial ERPs with differential latency variabilities. The data are single trials ERP sorted by P3 latencies from electrode CPz of a single subject from a face recognition task (Rellecke,

Sommer, & Schacht, 2012).

2. Summary of previous solutions

The pursuing of a more accurate characterization of brain response based on addressing the latency jitter issue has a long history and is still advancing. The earliest relevant attempt dates back to half a century ago (Woody & engineering, 1967). Woody pioneered the method of identifying the single trial latencies of ERP components (mainly late component) and re-synchronizing single trials according to the estimated latencies with the aim of obtaining a 'rectified' ERP. Since then, various methods and approaches have been attempted. In the following, I concisely reviewed this vein of research. I only focus on methods that aimed to correct ERP waveforms that are blurred due to latency jitter. The correction will thus mainly benefit research works concerning the unfolding of neural cognitive activities in response to external input, such as neural dynamical modellings, mental chronometry, and studying of separate sequential neural cognitive stages, and so on. I do not cover ERP signal processing methods that aim to extract EEG information by other means but not focusing on the depiction of ERP waveforms, such as time frequency analysis, Laplacian filter, blind source separation, or advanced statistical analysis like random stimulus effect modelling (Westfall, Nichols, & Yarkoni, 2016)) that aimed to improve or rectify the statistical relationships between neural signal and external factors.

2.1 Averaging after resynchronization

Resynchronization is the core procedure for dealing with the asynchrony problem. The basic procedure is to identify the single trial latencies of a ERP component (See 2.2) and re-synchronize single trials to the identified latencies instead of to stimulus onsets and obtain a new ERP (Patterson et al., 2000; Pomalazaraez & Mcgillem, 1986; Woody & engineering, 1967). This approach was the earliest attempt and has been applied to answer research questions that do not require very fine-grained examination of various ERP sub-components, such as, in the cases only concerning jittering of large ERP components (Kutas, Mccarthy, & Donchin, 1977; Sekar, Findley, & Llinas, 2012; Spencer, Abad, & Donchin, 2000; Yu, Dube, & Donchin, 2017). However, resynchronization of single trials to any other set of latencies is as problematic as stimulus-locked averaging, because an ERP is not a single fixed-shape component that are deterministically elicited by single time event, but rather, it could contain multiple components not locked to each other (Fig 2). For instance, a reaction time (RT)-locked average ERP will simply blur stimulus-locked portions (Berchicci, Spinelli, & Di Russo, 2016) (Fig 2). The multi-compositional nature of ERP with differential trial-to-trial latency variability makes simple resynchronization of single trials an insufficient approach to addressing the ERP asynchrony issue. Driven by this, methods that decompose ERP into multiple components with differential trial-to-trial variability have been developed, which will be reviewed later.

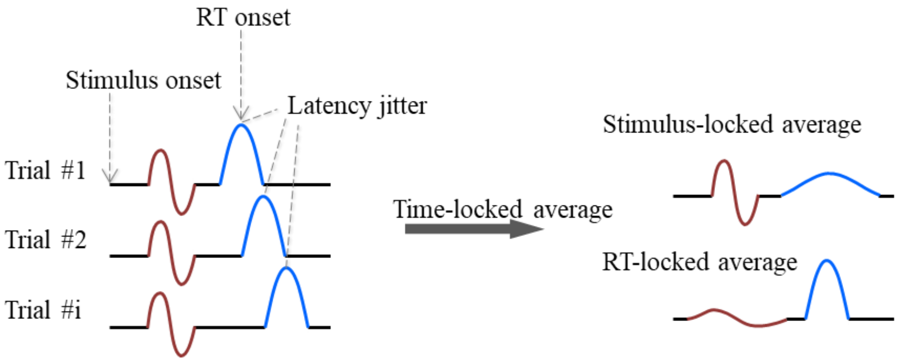

Figure 2. Dilemma of representing neural response by trial averaging. The red and blue component represents two components that are temporally locked to different events (e.g., stimulus onsets and RTs). Averaging the single trials to either event will blur the representation of the component that is locked to another event.

2.2 Single Trial Latency Estimation

Resynchronization requires single trial latency estimation. Various methods of single trial latency estimation have been proposed, differing in algorithm complexity and theoretical basis. Some examples are simple peak-picking in combination with temporal and spatial filtering for de-noising (Gratton, Kramer, Coles, & Donchin, 1989; Quiroga & Garcia, 2003), cross-correlation based template matching (Gratton et al., 1989; Woody & engineering, 1967), and maximum likelihood approach assuming the Gaussianity of background noise spectrum (Jaskowski & Verleger, 1999; Tuan, Mocks, Kohler, & Gasser, 1987). The pros and cons of each type of methods have been well elaborated in another review (Ouyang, Hildebrandt, Sommer, & Zhou, 2017). The key challenge lies in the heterogeneity of ERP components which renders the complication as to which component's latency is to be measured. Single trial ERPs consist of low-level/exogenous (e.g. P1/N1) and high-level/endogenous components (e.g., P3/N400), functional oscillations, spontaneous activity and noise, and interactions between them. Clearly defining (and thus refining) the component to be estimated is in most cases more important than the algorithms used for the single trial latency estimation (Ouyang et al., 2017). For example, to characterize the single trial morphology and latency of P3, deliberate temporal and spatial filtering settings have to be applied (Gratton et al., 1989; Jaskowski & Verleger, 1999, 2000; Mccarthy & Donchin, 1981) to avoid poor measurement of the latency in the raw data that is embedded with profound oscillations. But in characterizing early components like P50, P1 or N1 latency, the temporal and spatial settings can be completely different (Milne, 2011; Patterson et al., 2000).

2.3 ERP decomposition and reconstruction

As different clusters of ERP sub-components appear to display different degrees/features of latency jitter (Tzyy-Ping Jung et al., 2001), it has been proposed that these components can be separated based on their distinct latency variability feature and relevant methods have been developed. The earliest attempt was simply to separate an ERP into a stimulus-locked component cluster and a response-locked component cluster based on markers of stimulus onsets and reaction times, which can be done with mathematical derivation (Bardy, Van Dun, Dillon, & Cowan, 2014; Dandekar, Privitera, Carney, & Klein, 2012; Hansen, 1983; Smith & Kutas, 2015a, 2015b; Takeda, Yamanaka, & Yamamoto, 2008; J. Zhang, 1998). In essence, such decomposition methods were based on general linear model (GLM), where the time markers serve as the regressors (independent variables), the raw EEG data serve as the dependent variable, and the waveform associated with each regressor is the coefficient vector to be solved in the GLM framework.

However, as neural cognitive processes are functionally modular – they can be divided into different stages, for example, perception, central cognition, and response/execution (Hurley, 2001), RT is not sufficient for capturing the interval variability. In fact, no external markers are available for indicating the interval latency jitters of different stages of neural activations. Motivated by this issue, researchers have proposed several methods to decompose ERP without fully relying on time markers (G. Ouyang, W. Sommer, & C. S. Zhou, 2015b; Takeda, Sato, Yamanaka, Nozaki, & Yamamoto, 2010; Truccolo et al., 2003; Wu et al., 2014). The basic approach is to estimate the latencies of the components (see the section above), thus creating 'time markers' that are to be fed into the time marker-based ERP decomposition methods, as described above.

Upon the successful decomposition of ERP into different components with different latency jitter, an improved representation of ERP can be achieved by summing up them together at their respective most probable latencies, thus forming an in-principle more accurate representation of the dynamic neural response at the single trial level (Fig 3b). An analog of this issue is shown in Fig 3a: when we directly average multiple facial pictures we get a blurred and not-so-meaningful version; but if we were able to parameterize the feature of each element (eye, mouth, nose, etc.) and use the average parameters to construct a new face, this face would be far more meaningful for our understanding of the facial structure averaged from different individuals than the blurred version (Fig 3a). Similarly, ERP can in reconstructed following the same principle (Fig 3b) by incorporating the aforementioned decomposition methods.

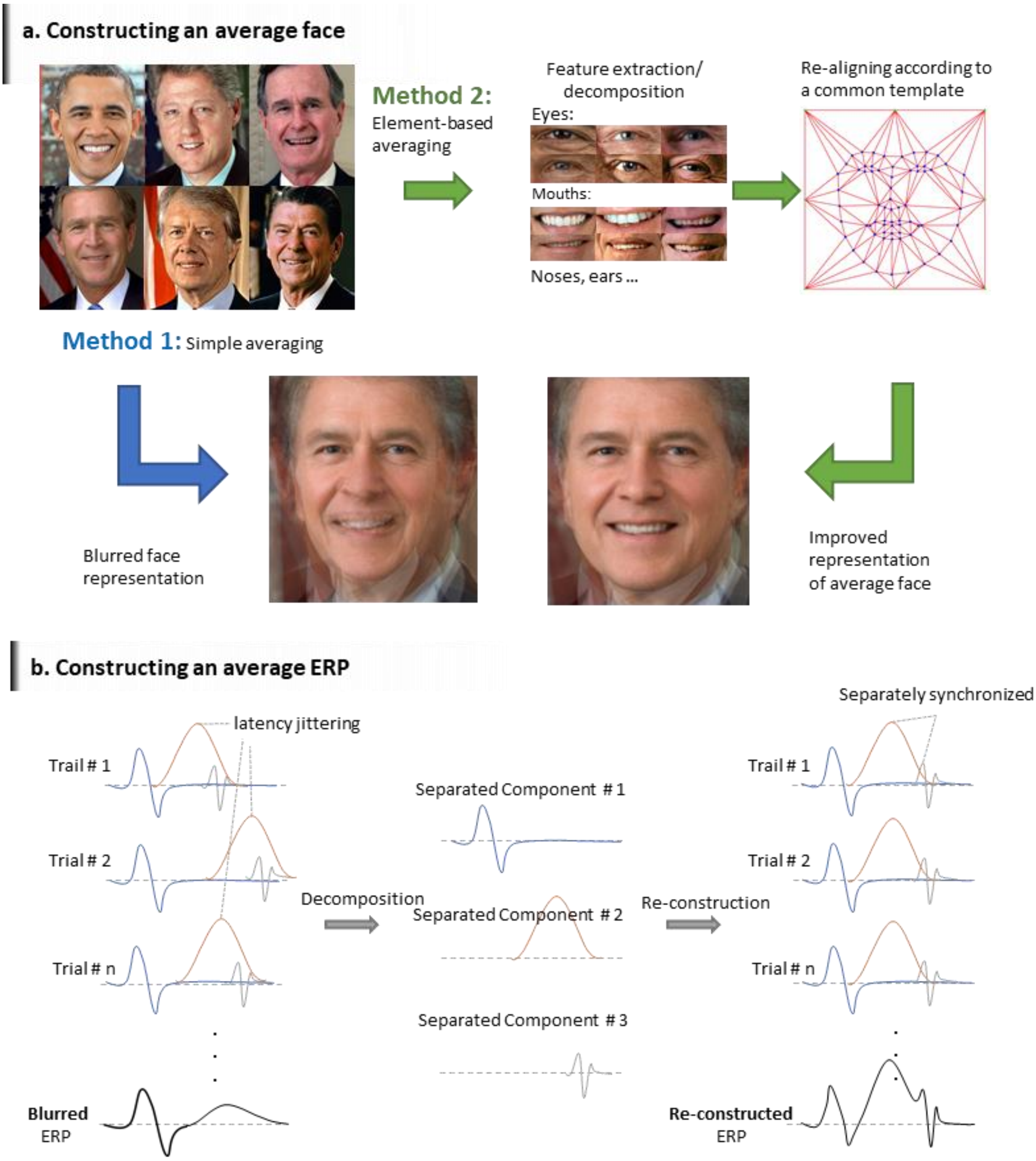

Figure 3. Obtaining a more accurate and meaningful neural dynamic response pattern by jitter-corrected ERP reconstruction. (a) Face averaging as a conceptual analogue of ERP reconstruction. Different faces can be aligned by the eye positions and averaged, which will lead to a blurred face picture (left). Or different facial elements (eyes, noses, mouths) can be separately parameterized and aligned, which will lead to a meaningful average face picture (right). (b) Following the similar idea of face averaging, ERP sub-components can be separated (by decomposition methods) and re-aligned to obtain a reconstructed pattern that more meaningfully represents a likely response pattern in single trials.

It is worth noting that the methods mentioned above are all relying on utilizing the latency variability information to decompose ERP, and they all operate on EEG data that has been preprocessed with major artifacts removed. Different from this type of methods, there is another highly noticeable class of decomposition methods that could also be adopted for improving brain response characterization by tackling the latency jitter issue: blind source separation (BSS). BSS methods assume that independent neuronal or non-neuronal signal generators simultaneously contribute to scalp EEG. Various algorithms with different theoretical bases have been developed to decompose EEG data within this framework (Albera et al., 2012; Lee, Girolami, & Sejnowski, 1999; Uriguen & Garcia-Zapirain, 2015). The assumption of source independence is reasonable in view of the heterogeneity of EEG data and its high susceptibility to various non-neuronal artifacts. Its relevance to the ERP latency jitter issue is that different independent sources may account for different ERP subcomponents with different degrees of latency variability. If this is the case, each independent component (IC) can be synchronized to their own latencies (given that the single trial latency estimation is reliable) to generate jitter-corrected source ERPs that can more precisely describe the brain response. In fact, using BSS to address the latency jitter issue has been touched upon based on the *infomax* ICA algorithm (T. P. Jung et al., 2001). In that work, the ICs were classified into two types: those that were locked to stimulus onsets and those that were with variable latencies associated with response times. Through resynchronization of different ICs, a reconstructed ERP can be generated with latency jitter compensated for. The rationale for such ICA-based decomposition and reconstruction of ERPs after correction of all latency variabilities is clear. The remaining question is that different resultant ICs have yet to be proven to capture only a single component with a specific type of jitter (e.g., ideally, an IC mainly capturing the latency-variable P3 component should not contain the latency-stable P1/N1 components). This issue could be challenging but it is worthwhile to further investigate this line in the future development.

2.4 General issues and challenges

Considering the ample evidence, detailed demonstration, wide recognition and discussion of the latency jitter issue in ERP research (D'Avanzo, Schiff, Amodio, & Sparacino, 2011; T. P. Jung et al., 2001; Knuth et al., 2006; Kutas et al., 1977; Lau-Zhu, Fritz, & McLoughlin, 2019; Ouyang et al., 2017; Sassenhagen & Bornkessel-Schlesewsky, 2015; Saville et al., 2015; K. B. Walhovd, H. Rosquist, & A. M. Fjell, 2008), it is surprising that no well accepted tool for correcting latency jitter has come into play in the community. Researchers are still largely using trial-averaged ERP as a representation of dynamic brain response. A robust framework for tackling the latency jitter issue and improving the representation is strongly needed. In the following, I summarize some major issues and challenges previous methods have faced before presenting the ReSync method and toolbox.

Methodological complication. Probably no method can be simpler than trial-averaging in the arena of EEG research. Although having inherent limitations, trial-averaging is based on a much simpler assumption than that of decomposition methods that separate ERP into two (Hansen, 1983; Takeda et al., 2008), three (Knuth et al., 2006; Ouyang et al., 2015b), four or higher number of components (Wu et al., 2014), up to the number of electrodes (Lee et al., 1999). The introduction of component multitude complicates the interpretation and reasoning of the method-generated results due to the implication of theoretical and methodological factors in the results. Additionally, component multitude brings challenges in new analysis such as multivariate analysis, classification and clustering, and high-dimensional feature extraction, which leads to a more complicated analysis scenario than trial-averaging and could give birth to epiphenomenon problems. This could be one of the reasons that hinders the application of methods for addressing the jitter issue.

Theoretical problems. Decomposition of ERPs[1] is an inverse problem. A critical question concerning decomposition is whether it is theoretically worthwhile and meaningful. As an analogy, one can cut an apple into two halves or peel a banana to separate the peel and pulp. The latter is clearly more 'theoretically' meaningful. ERP components may or may not be composed of multiple components in the way that various methods assume. Without proper theoretical or statistical assessment, it is difficult to tell whether a method improperly decomposes the ERP. For instance, the early components (e.g., P1) are more associated with low-level sensory processing

[1] Decomposition of ERP is different from decomposition of EEG. The former operates on the brain response component (ERP) triggered by external events, whereas the latter directly operates on the raw EEG signal with much more heterogeneous components including various artifacts.

(Tobimatsu & Celesia, 2006), and the late components (e.g., P3) are more related to high order cognitive processing (Twomey, Murphy, Kelly, & O'Connell, 2015). It would be ideal if these two types of components were exclusively separated into different components, but decomposition methods are not necessarily able to separate them cleanly because the expectation that they can be separated are based on a neurocognitive perspective, which is blind to methods that are only based on quantifiable data features and relations (e.g., Gaussianity, correlation, statistical independence). So, whether the separation is theoretically proper remains a non-trivial and open issue where conventional ERP researchers would not easily invest effort in investigating.

In some cases, the decomposition method even gives rise to theoretically unacceptable solutions, one example is noise amplification which has a mathematical root (Ouyang et al., 2015b). Specifically, when two kinds of markers (e.g., stimulus, RT) have very small inter-marker jitter across trials, the mathematical solution gives rise to two complementary waveforms (with large amplitude) in the two decomposed components that are biologically implausible (Ouyang et al., 2015b). This is due to the close-to-singularity of the covariance matrix of the two regressors (Ouyang et al., 2015b). Similar issues exist in dipole source localization when different dipole sources have a high spatial correlation, in which case the source temporal activity will have complementary patterns resembling amplification of noise (Wolters, Beckmann, Rienacker, & Buchner, 1999). This issue requires introduction of regularization which brings another layer of complication that may deter most researchers. Apart from the above, there are other theoretical issues in ERP decomposition that need not to be concerned in trial-averaging, for example, the linearity assumption about the constitution of the separate components, the multiple comparison issue in statistical analysis when a large number of separate components are analyzed instead of only one average ERP.

Technical complication. Currently, researchers focusing on trial-averaged ERPs can easily conduct data analysis in various well-developed software. Accessing the landscape of brain responses in single trials is technically more demanding and is thus usually limited to smaller groups of experienced researchers. Developing tools for single trial and inter-trial characterization, analysis, and modelling involves a much higher degree of complexity in parameters and algorithms than for average-based analysis. Many latency jitter-tackling methods are only available in the original paper or relatively complicated form of codes or toolboxes (Ouyang et al., 2015b; Takeda et al., 2010; Truccolo et al., 2003; Wu et al., 2014).

As such, methods for tackling the latency jitter issue have certainly not permeated the ERP community despite the wide recognition of the need. On a positive note, single trial ERP analysis has received increasing attention driven by the rich functional implications of trial-to-trial variability (A. G. Collins & M. J. Frank, 2018; Dinstein, Heeger, & Behrmann, 2015; Stokes & Spaak, 2016; Trenado et al., 2019). Hitherto single-trial ERP analysis has been mostly based on statistical features across trials, but has much less focused on improving the characterization of the ERP dynamic waveform, which is essential for studying neural cognition at a mechanistic level. Integrating the various issues summarized above, in the next sections I present the ReSync method and toolbox aiming to address some of the aforementioned issues based on a simple theoretical and methodological framework.

3. ReSync – A Simple method to correct ERP jitter

Considering the aforementioned complication in using ERP decomposition for addressing jitter issue, the scope of ReSync will not cover decomposed or separated ERP sub-components. The aim of ReSync is to simply obtain a jitter-corrected ERP in a format that is totally identical to standard ERP, namely, trial-averaged ERP. This will certainly limit its utility in investigating ERP sub-components with different functional and cognitive signatures which many other methods and tools were developed for, many of which have demonstrated great merit in this respect, e.g., (Delorme & Makeig, 2004; Dien, 2010; G. Ouyang, W. Sommer, & C. Zhou, 2015a). But it will meet the needs of those researchers who are simply concerned with the latency jitter issue and want to correct them without bringing additional complications.

However, as ERP contains different components with different jitter (Fig 1d), it is impossible to correct one without affecting the other (Fig 2) without decomposing it. Therefore, ReSync will still incorporate decomposition in its internal steps. Here I first describe the general principles of ReSync before describing the theoretical and technical parts.

1. The purpose of ReSync is to provide a jitter-corrected ERP.

2. In a typical scenario, a researcher would identify an ERP component (e.g., P1, N1, P3, or N400, etc) that is affected by latency jitter. The researcher would then need to specify a time window for ReSync to estimate the single trial latencies (see procedures later). This set of latencies will be used to isolate the latency-varying component from single trials, obtain its jitter-corrected form, and sum it back with other components to obtain a jitter corrected ERP (Fig 3b). This way will not affect (blur) other components (like what is shown in Fig 2).
3. After correcting the first component, a new time window can be specified to correct a second component without affecting the rest. The procedure can go on and on. A demonstration of the procedure will be illustrated later.

3.1 ERP decomposition and reconstruction

This section will describe the theoretical foundation and technical details of ReSync. Assuming that a single trial contains only an activation component lasting for a fixed period of time, an EEG trace from an electrode can be expressed as:

$$EEG(t) = \sum_{\tau=1}^{T} C(\tau)X(t-\tau) + \varepsilon. \tag{1}$$

where C denotes the event-elicited component covering sample points from $\tau = 1$ to T, X is a timing function (also called stick function in neuroimaging field (Pisauro, Fouragnan, Retzler, & Philiastides, 2017) coding the events by denoting event occurrence time points as 1 and all other time points as 0, and ε denotes noise.

If there are two activation components existing in every single trial, temporally locked to different events, the EEG trace is then:

$$EEG(t) = \sum_{\tau=1}^{T_1} C_1(\tau)X_1(t-\tau) + \sum_{\tau=1}^{T_2} C_2(\tau)X_2(t-\tau) + \varepsilon. \tag{2}$$

A typical example is that C_1 is the stimulus-locked component and C_2 is the RT-locked component, in which case X_1 and X_2 are the timing functions for stimulus onset and RT, respectively.

Equation (2) can be written in a matrix form:

$$\mathbf{EEG} = \mathbf{X} \cdot \mathbf{C} + \varepsilon. \tag{3}$$

With the information of the time markers **X**, the least square error-based solution of the components can be expressed as (Dandekar et al., 2012):

$$\mathbf{C} = (\mathbf{X}^{\boldsymbol{t}}\mathbf{X})^{-\mathbf{1}} \cdot \mathbf{X}^{\boldsymbol{t}} \cdot \mathbf{EEG}. \tag{4}$$

Based on this solution, each component can be isolated (Fig 4), given that the covariance matrix $(\mathbf{X}^{\boldsymbol{t}}\mathbf{X})$ is not singular. When the covariance matrix is close to singularity (i.e., when the inter-component latency variability approaches zero), the background noise will be severely amplified and injected to the solution (Ouyang et al., 2015b), leading to a divergent solution that is biologically implausible and unacceptable. The noise amplification issue, however, does not affect the reconstruction procedure as shown later.

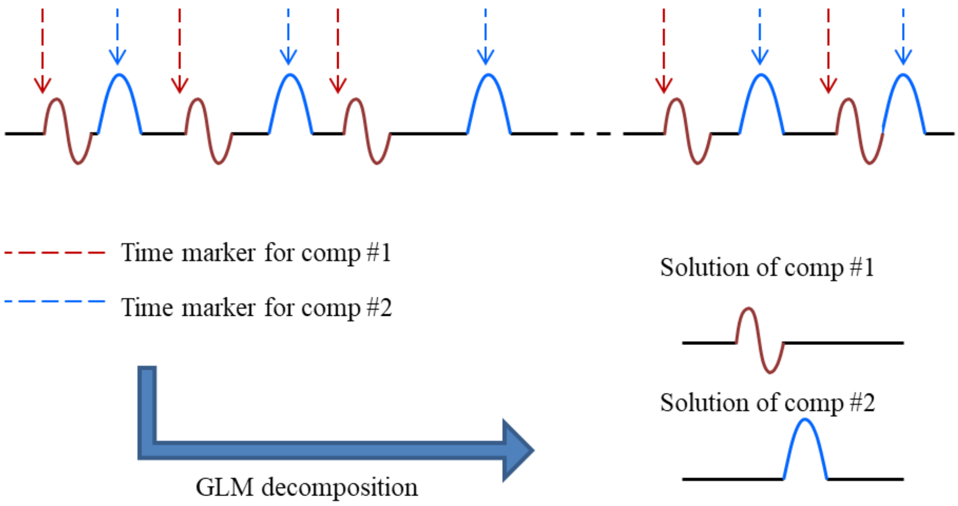

Figure 4. Decomposition of overlapping ERP components using GLM with the time markers of different components being regressors.

In the context of a stereotypical ERP experiment, the timing function X_1 is usually for coding the stimulus onsets, thus for deriving stimulus-locked component C_1 (If only one component is assumed, C_1 is the standard ERP). In the ReSync framework, new components with non-stimulus locking features are to be extracted and separately re-synchronized (so as not to affect the stimulus locking ones). The latency-variable component is not confined to late ones but can also be the early ones, e.g., P1, N1. If components with latency jitter are assumed to exist, their timing functions need to be provided. In a generic case, the timing (latencies) can be estimated. In ReSync, the method of latency estimation of the latency-varying component is based on cross-correlation-based template matching. Basically, the template is derived from the average waveform within the specified time window. The template is then moved both left- and rightward until a peak value of correlation between the template and single trial is found. This peak will be used to determine the lag (latency) of the single trial activity with respect to the template. The whole set of latencies are then fed to the decomposition procedure. It has to be noted that a low-pass filtering on the cross-correlation curve is crucial as it will allow relevant peak to be found. For example, when searching a P3-like component, it is used to be suggested to use around 4 Hz (Gratton et al., 1989; Jaskowski & Verleger, 1999, 2000; Mccarthy & Donchin, 1981); when searching a P1/N1 complex-like component, it can be set to be around 10 Hz (or higher) as the component is much sharper. However, as there is great variability across individuals and experiments, using a fixed value to low-pass the cross-correlation curve is not ideal. I proposed an automatic identification of the low pass filtering frequency as described below.

As ERP component clusters (e.g., P1/N1 complex, P3) displays a clear and structured waveform in the averaged time course, there should be a dominant frequency each component (cluster) possesses. Visually, P1/N2 seems to be around 10 Hz, and P3 around 2-4Hz, but very much depending on data specificities. The dominant frequency, once is known, can be used to low-pass the cross-correlation curve in the latency estimation procedure. We can estimate the dominant frequency in this way: first transform each single trial (within a specific time window, linearly detrended) into frequency domain using Fourier Transform, then average the Fourier coefficients (in complex values) across single trials and identify the frequencies with maximum modulus from the average. The identified peak frequency f_0 will be regarded as the dominant frequency and f_0 + 1 Hz will be used to low-pass the cross-correlation curve (+1 is from consideration of trial-to-trial fluctuation). In this case, the dominant frequency can be automatically determined, and this value is saved in the ReSync output.

After the two components, namely, stimulus-locked and latency-varying component were isolated based on (4), the ERP can be reconstructed in a way that the latency-varying one is represented in a de-blurred form as shown in Fig 3b. If the researcher considers that there is still other latency-varying component in other time window, a new time window can be specified and a new set of latencies can be estimated, and the ERP reconstruction can be conducted again. The detailed instruction is described in the online manual. Below I use an example to describe the basic implementation procedure.

3.2 Simple Operations in ReSync Toolbox

The ReSync toolbox can be installed as an extension in EEGLAB toolbox (Delorme & Makeig, 2004). The basic interface is shown in Fig 5a. The data for demonstration is from a facial recognition experiment (Rellecke et al., 2012). User simply needs to select the electrode and time markers from which ERP will be generated. If multiple electrodes are selected, the data will be averaged over the selected electrodes. After the selection, the average ERP as well as the single trial data can be plotted (Fig 5b) for examination and for identification of proper time window(s) for ReSyncing.

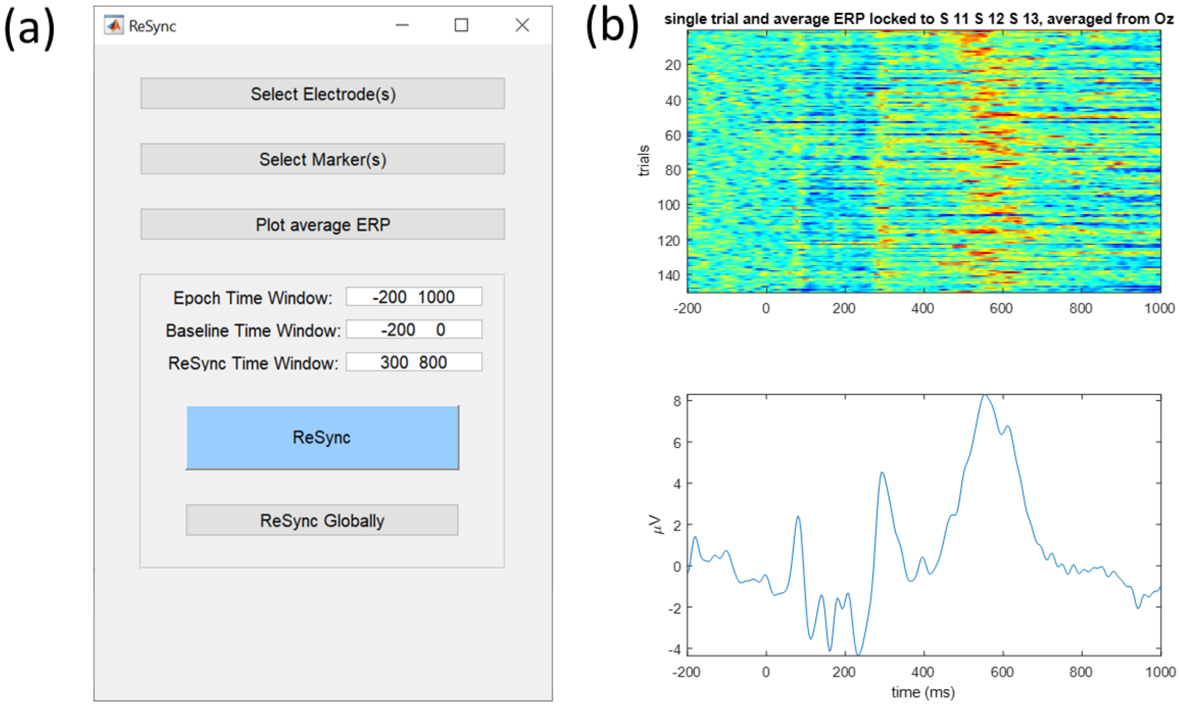

Figure 5. Interface of ReSync toobox (a) and the visualization of single trials and average ERP for determining the time window for jitter correction (b).

For the next step, user needs to specify a key parameter for ReSyncing: ReSync time window – the time window where the single trial jitter is to be corrected. In the illustrated example shown in Fig 5b, we see a very jittering component within 400-800 ms, so the ReSync time window can be set to be from 400 to 800 to correct the jitter of this late positive component. After specifying all parameters, clicking ReSync button will generate the ReSync results as shown in Fig 6. The ReSync result is informative in that it provides the original single trials sorted by estimated latency (Fig 6a), the highlighted latency-varying single trial activities (Fig 6b), and jitter-corrected single trials (Fig 6c), the jitter-corrected ERP as well as its comparison with the original one (Fig 6d). There are three major descriptive points from Fig 6 that are worth to be stressed: 1) The latency estimation appears to be reliable as shown in the sorted trials (Fig 6a b); 2) The correction of jitter in the specified time window (400 ms to 800 ms) still preserve the jitter features in other time windows (e.g., early ones, see Fig 6c); 3) The correction in the average waveform is also exclusively taking effect in relevant window (Fig 6d).

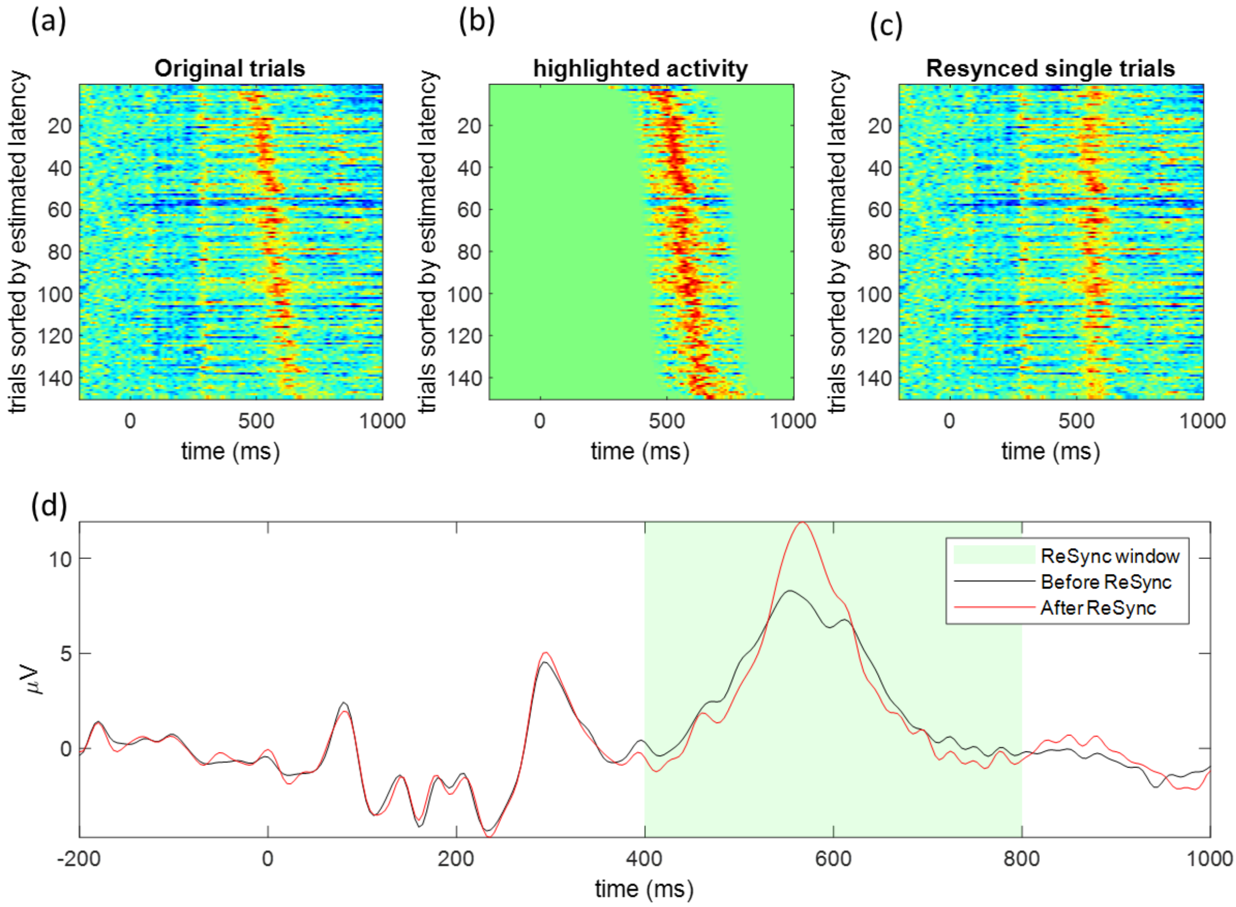

Figure 6. Visual summary of Resync results. (a) Single trials ERP sorted by estimated latency. (b) Highlighted component activities that are with latency jitter. (c) Jitter-corrected single trials. (d) Comparison of standard average ERP and jitter-corrected ERP (specified ReSync time window is indicated by the light color background).

Likewise, the latency jitter issue can occur in the early time window as well, and its functional relevance has been studied (Kovarski et al., 2019; Magnuson, Iarocci, Doesburg, & Moreno, 2019; Milne, 2011). To serve as a demonstration, we can specify the time window 200-400 ms encompassing the early component in the sample data. In this case, ReSync corrected the ERP jitter only within this window without affecting activities in other times (Fig 7).

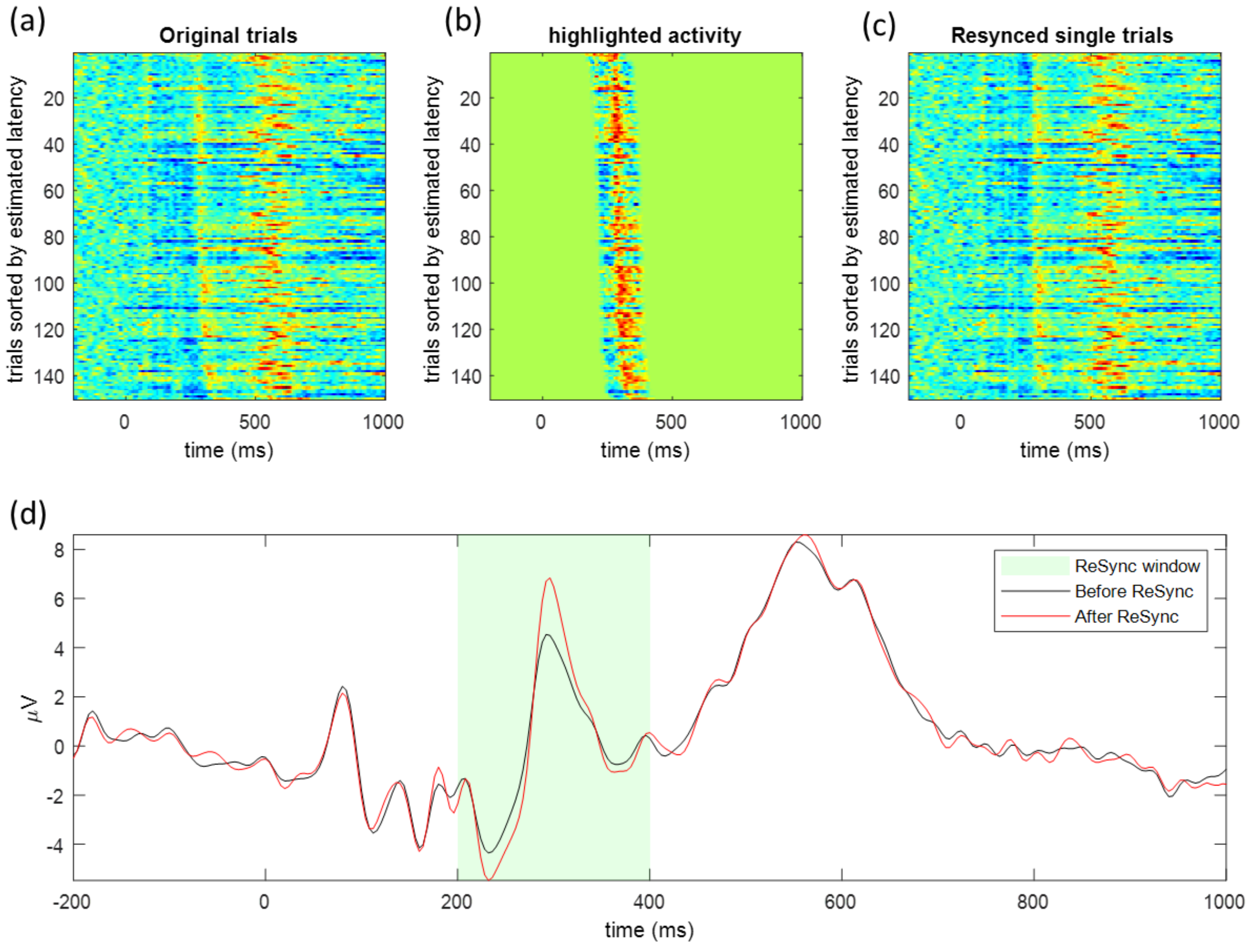

Figure 7. Visualization of Resync results for correcting jitter in early time window.

The correction of multiple components can be done iteratively (each step overwriting the previous EEG data). The final effect of correcting the above-mentioned two components were shown in Fig 8, which shows that the jitter in both 200-400 ms and 400-800 ms were corrected. Detailed implementation procedures were described in the online manual (https://github.com/guangouyang/ReSync).

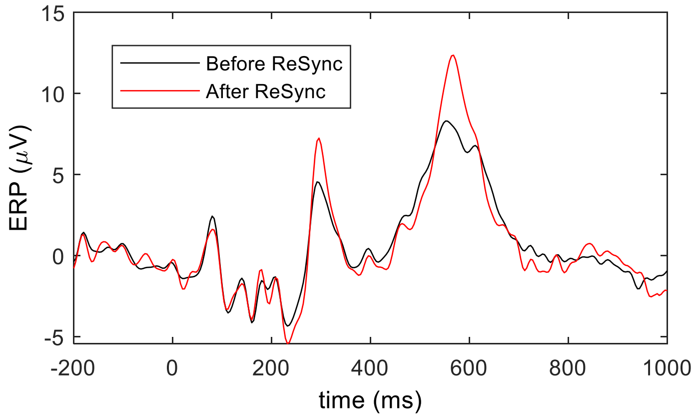

Figure 8. Correcting jitter in both early and late time windows.

Although the electrode(s) need to be specified for estimating the latency jitter, the ReSync correction can be done on the entire scalp, namely, all electrodes, not just on the specified ones. This is because that, due to high volume conduction, ERP component's signal are usually widespread. Therefore, all electrodes' ERP should be corrected for jitter using the single trial latencies estimated from the specified electrode(s) where the component is strongest. If an electrode contains very little activation of the component of interest (e.g., P3), the correction would only have minimal change to the original ERP on this electrode. Correcting all electrodes can be simply implemented by clicked the button 'ReSync Globally'. After that, the EEG data will be modified (with jitter corrected) and user can choose to overwrite the original EEG dataset or create a new one. The jitter-corrected new EEG dataset has an identical format with the original one. Users can do all the subsequent analysis just like what they would do on standard ERP. They can also export the data and load them into other software.

To sum up here, ReSync provides an easy-to-use signal processing tool to correct ERP waveforms that are blurred by latency jitters by re-synchronizing each latency-varying components without affecting others. The respective component synchronization was achieved by first decomposing the ERPs and isolating the latency-varying component from the rest, and summing back the de-blurred form of latency-varying one to the rest (Fig 3b). The decomposition is automatically conducted as internal steps in the processing pipeline, which is not apparent in the final result where only the jitter-corrected data is presented in a same form with standard ERP. The entire procedure of ReSync is quite straightforward and practical. In the next section, I will evaluate and validate this method from different aspects.

4. Evaluation and Validations

4.1 Effect of Signal-to-Noise Ratio and degree of latency jitter to the performance of ReSync

One of the most crucial factors that affects most signal processing method is signal-to-noise ratio (SNR). In ReSync, SNR mainly affects the latency estimation procedure. Overly strong background noise will lead to arbitrary latency identification (because noise can override/mimic ERP components) and thus worsen all the subsequent processing – garbage in garbage out. Therefore, it is important to evaluate the SNR of ERP data and how it determines the performance of ReSync.

To examine this, I simulated single trials ERP data with systematically assigned SNR

(Fig 9). Specific parameters are as follows: trial number: 50; sampling rate: 1000 Hz; epoch length 300 ms; ERP component: a half-sinusoidal shape spanning 100 ms; type of background noise: 1/f noise. The SNR of the simulation data will be systematically varied. SNR is defined in a way that is also easy to be calculated from real ERP data. The signal is defined as the ERP, and the standard deviation of it is denoted as SD(ERP). The noise is defined as the spontaneous EEG signal overriding on ERP in each single trial. The standard deviation of the noise (assumed to be stable) is denoted as SD(noise). SNR is then SD(ERP)/SD(noise). To estimate the noise strength, we can first invert the signs of half (randomly drawn) of the trials and average all the trials. In this way the ERP is effectively cancelled out. The SD of the resultant average waveform from the half-inverted trials is denoted as σ_1. SD(noise) will be calculated as $\sigma_1 \times \sqrt{n}$ where n is the number of trials. Denoting the SD of the standard trial-averaged waveform as σ_0, SD(ERP) will be calculated as $\sqrt{\sigma_0{}^2 - \sigma_1{}^2}$. Based on the above-described procedure, SNR can be obtained in both simulation and real ERP data. The calculated SNR from the sample simulation data is shown above Fig 9d.

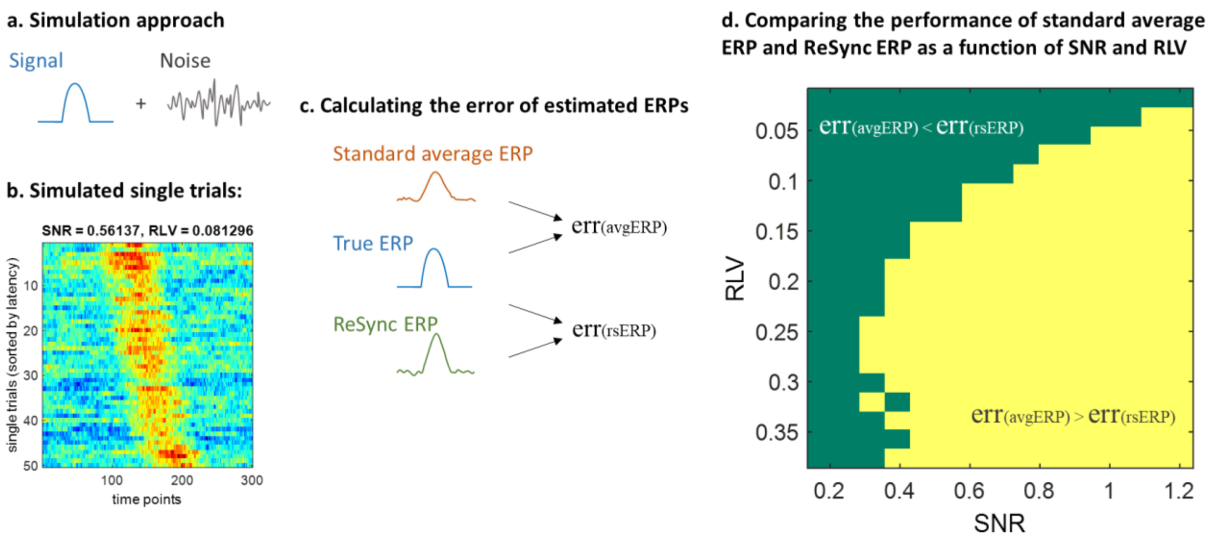

Figure 9. Evaluating the performance of ReSync on simulation data with

different parameters. (a) The composition of simulation data. (b) Example of simulated single trials. (c) Calculating the estimation error of standard average ERP and ReSync ERP as compared to the ground truth ERP. (d) Comparing the performance of standard average ERP and ReSync ERP.

To evaluate the performance of ReSync in the simulation data, I used a very simple notion: the difference between ReSync ERP and the ground truth ERP should be smaller than the difference between standard average ERP and the ground truth ERP – if not, it does not make sense to ReSync the ERP (namely, to correct the jitter). The difference is calculated as the sum squared error between the ground truth ERP (half-sin) and estimated ERPs. Here the estimated ERP has two versions: standard average ERP and ReSync ERP. I denote these two versions of error function as err(avgERP) and err(rsERP). If err(rsERP) < err(avgERP), correcting the jitter is better than not correcting it (vice versa). Reader might ask how it is possible that correcting the jitter leads to a worse estimate of the ground truth ERP? This is because when the SNR is too low, the correction could become arbitrary (due to arbitrarily estimating the latency jitter) which may lead to a worse estimation than simple averaging.

Apart from SNR, another factor that is worth to consider is the degree of latency variability. Intuitively, if latency variability is small, the data is less needed to be jitter-corrected, thus the correction by ReSync will more likely to perform worse than standard average ERP. Therefore, I added latency variability as another dimension to examine the performance of ReSync. The evaluation of ReSync's performance under different features/quality of data is for user to evaluate the necessity of using ReSync. However, different from SNR, the latency variability is not a quantity that can be directly translated from simulation to real data. In the simulation data, the latency variability is an arbitrary scale. The value of latency variability (e.g., SD) only makes sense when the component feature is considered. For example, in the simulation data, I can make the half-sin ERP component (Fig 9) as spanning 100 ms (map to around 10 Hz) or spanning 500 ms (map to around 2 Hz). The same value of latency variability for these two situations would differentially affect the performance of jitter correction. More specifically, a sharp component (with a high dominant frequency) with a fairly large latency jitter would make it necessary to correct its jitter, but a blunt component (with a low dominant frequency) with the same amount of jitter may not need to be corrected. This non-universality issue does not only exist between simulation data and real ERP data, but also exist between different types of ERP components (e.g., early and late components where early is usually sharp and late is usually blunt). Therefore, there needs to be a universal characterization of the degree of latency variability that is referable in real data application, preferably, a normalized measure such as Pearson correlation coefficient.

To address this issue, I proposed a measure called relative latency variability (RLV) that can be universally referenced. RLV is defined as the standard deviation of latency variability divided by the dominant wave period of the jittering ERP component. The dominant wave period is just the reciprocal of the dominant frequency (see above for how to determine it). Under this definition, the relative latency variability essentially reflects the degree of variability with respect to the width of the component, which is a unit-less value. After exploring the performance of ReSync also as a function of RLV in terms of whether the jitter-corrected ERP is closer to the ground truth ERP than is standard average ERP, user can simply calculate the RLV (which is automatically done in ReSync toolbox) and see whether their data should be jitter-corrected.

To wrap up, I will apply ReSync on the simulation data under various levels of SNR and RLV to draw the parameter sweeping map indicating under what parameter regions ReSync ERP is better, i.e., err(rsERP) < err(avgERP), and under what parameter regions standard average ERP is better, i.e., err(rsERP) > err(avgERP). Figure 9d shows the results of the binary map generated from 200 realizations. A clear boundary can be seen from Fig 9d, which is in line with intuition: when SNR is small, the latency estimation suffers from imprecision issue, thus standard average ERP wins; when RLV is small, there is less need to correct the jitter, doing so will likely to introduce error, thus standard average ERP also wins. The yellow region in Fig 9d is where the ReSync ERP is better which corresponding to high SNR and RLV. In the ReSync toolbox, the yellow region is defined as the intersection between the of plane SNR > 0.3 and the plane of SNR > 0.3 + 6×(0.175-RLV).

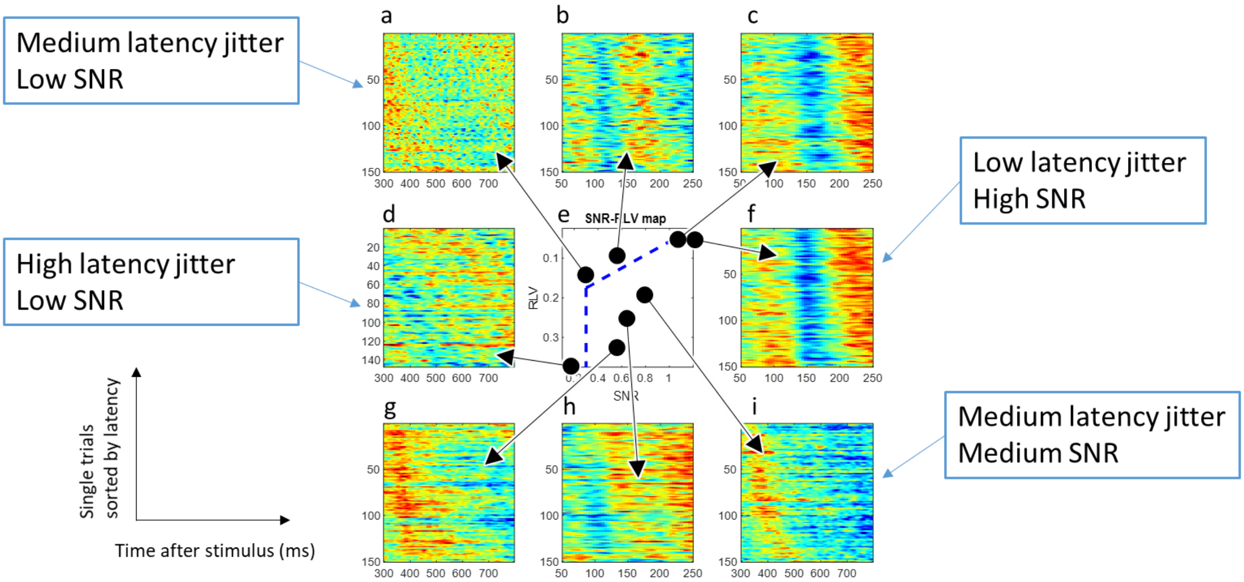

Figure 10. Example of single trial ERP data with different values of SNR and RLV. The values of SNR and RLV for each data panel are indicated by the dots on panel e. The blue dash line in panel e marks the boundary across which ReSync ERP is either better or worse than standard average ERP (see Fig 9d).

It thus important to know, where do the real data usually fall on the SNR-RLV map (Fig 9d)? To provide a straightforward perception, I exemplified several sets of single trial data from a face recognition task (Rellecke et al., 2012) that falls onto different positions of the SNR-RLV map (Fig 10). The actual data feature very well reflects the parameter values (lower SNR, messier data, higher SNR, clearer data). These sporadic examples demonstrated that there exist real EEG datasets that fall into the condition where jitter correction is recommended. To more systematically evaluate the scenario, I examined two datasets for all participants and different experimental conditions (dataset will be shared upon request). Dataset 1 (Delorme, Rousselet, Mace, & Fabre-Thorpe, 2004) is a visual categorization task where there were two conditions: target and distractor stimuli (14 participants). Dataset 2 (Rellecke et al., 2012) is a face recognition task where there were three conditions: happy, neutral and angry face stimuli (29 participants). I examined the SNR and RLV for both early and late components. The electrodes and time windows that capture the prominent feature of early and late components were determined based on grand average ERPs and were indicated in Fig 11a,d (individualized feature extraction may also be implemented, see Discussion). Fig 11 showed that in dataset 1, most participant fall into the area where ReSync corrected ERP is better than standard average ERP (the boundary is indicated by the blue dash line), for both early and late components. Dataset 2, however, showed features that mostly fall onto the boundary, indicating this dataset may not necessarily substantially benefit from ReSync correction.

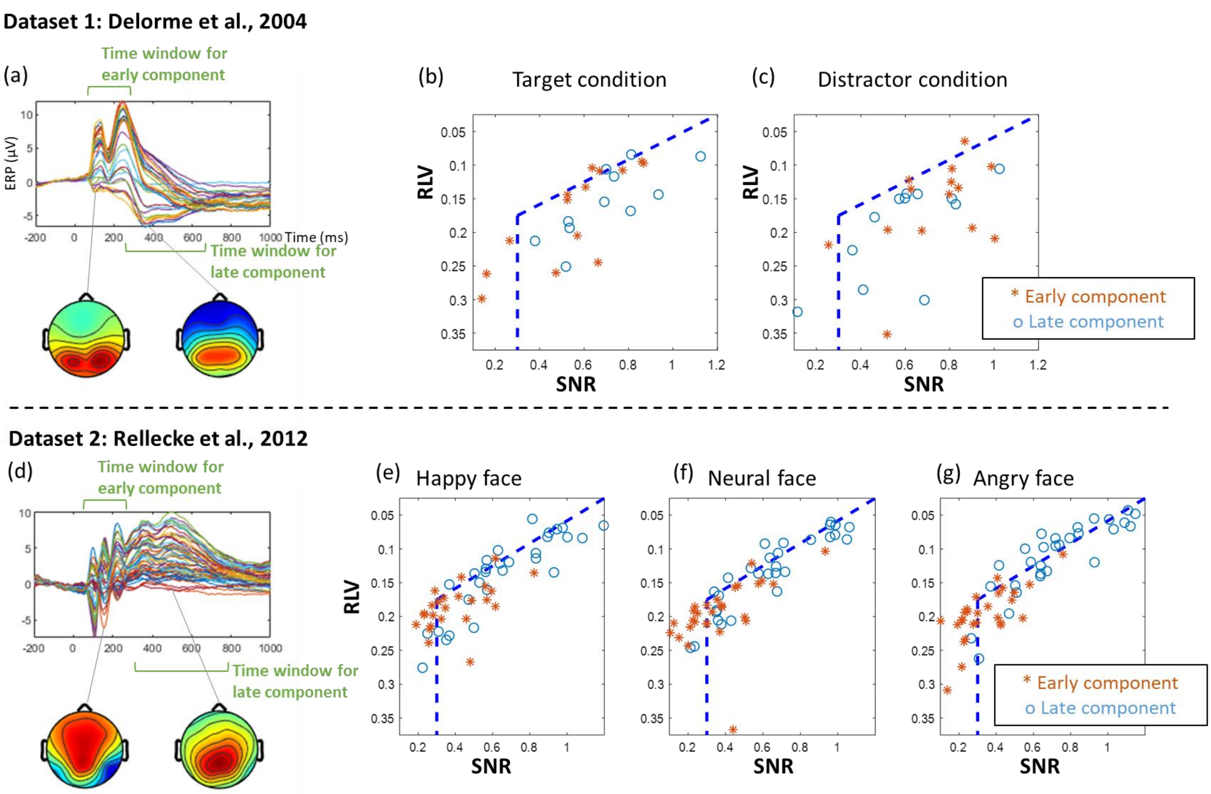

Figure 11. Distribution of SNR-RLV values of examined early and later ERP components for all participants from two datasets.

4.2 How does jitter correction affect statistical comparisons of ERPs?

One of the most important issues in ERP research is comparing ERP amplitudes between different conditions or groups (hereafter referred to as conditions). It is conceivable that latency jitter can substantially confound ERP amplitude effects (Ouyang, Sommer, & Zhou, 2016; K. B. Walhovd, H. Rosquist, & A. M. J. P. Fjell, 2008; Yu et al., 2017). One scenario is that jitters diminish ERP amplitudes as well as their between-condition difference. Another (opposite) scenario is that different degrees of jitter between conditions can produce spurious amplitude effect. In reality, both scenarios can be present, which complicates interpretation of neural effects. With that said, the outcome of ERP jitter correction by ReSync, in terms of weather it increases or reduces the between-condition ERP amplitude effects, is not one-directional. However, it is worthwhile to jitter-correct ERP (if the data quality falls into the yellow region in Fig 9d) to examine what the ERP effects would be like after the confounding jitter effects are effectively corrected.

To illustrate this issue, I applied ReSync to dataset 1 in which most participants show data feature falling into the yellow region (Fig 11). In this dataset, there exists amplitude effects in both early and later time windows (Delorme et al., 2004). In the experiment, the participants were simply required to categorize pictures that contain animal (target) or not (distractor). There were significant early ERP amplitude effects in occipital area and late ERP amplitude effect in parietal area (Delorme et al., 2004). ReSync was applied in both early and late time window (see time window determination in Fig 11).

As shown in Fig 12, the application of ReSync in this dataset yielded stronger amplitude effect in early time window, but no substantial change in later time window, as compared to standard ERP analysis. This probably reflects that the latency jitter is more similar between conditions in the early time window, ReSync thus restores stronger amplitude effect after correcting the jitter; and the degree of latency jitter may differ more in the late component (with weaker amplitude being associated with larger jitter).

5.5

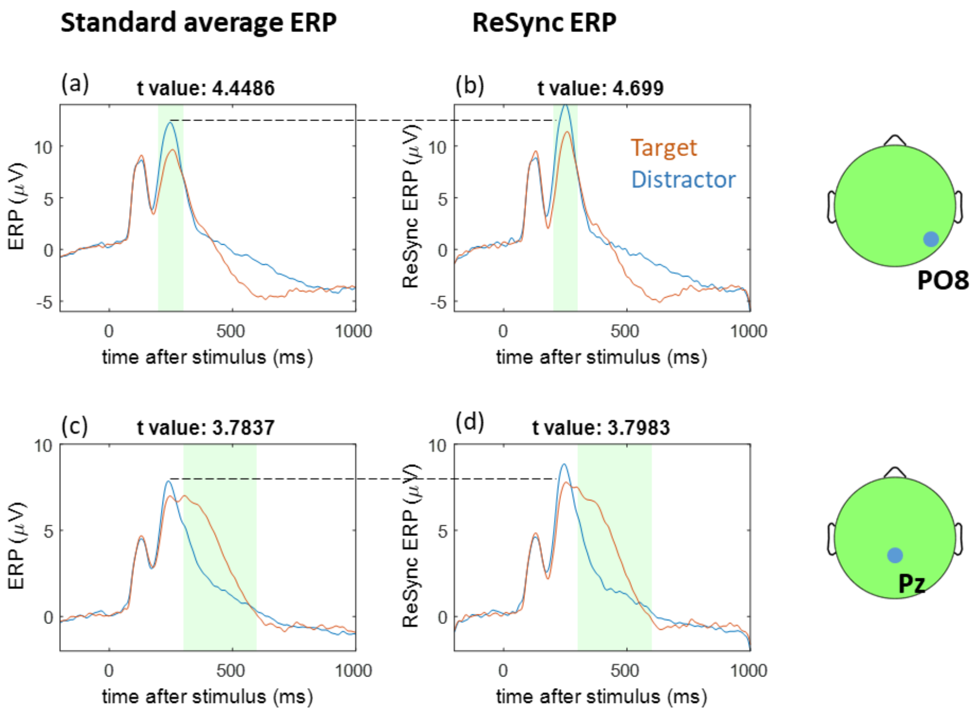

Figure 12. Change of amplitude effects between conditions before and after jitter correction. (a,b) For early ERP component. (c,d) For late ERP component. The t values are from simple t tests on the amplitude difference within the highlighted time windows.

5. Discussion

In this article, I have provided an overview of the long-standing latency asynchrony issue in brain research that has been relying on trial-averaged ERPs as a tool for depicting the dynamic brain responses, and the latest developments in methodology in addressing the limitations of trial-averaging approach. It is worth noting that the latency asynchrony issue is by no means a negligible technical limitation compromising data fidelity. Instead, it distorts neural representations in terms of (but not confined to) timing, behavioral effect, functional role, and anatomical feature (Bodmer, Muckschel, Roessner, & Beste, 2018; Miller, Ulrich, & Schwarz, 2009; Yang et al., 2017; D. D. Zhang, Ding, Wang, Qi, & Luo, 2015). With the advancement in signal processing techniques and theoretical modelling, the limitation that latency asynchrony imposes on brain response characterization is being progressively addressed. I have presented a method, ReSync, that can be used to remedy the standard ERP by correcting jitter-caused distortion. ReSync is an easy-to-implement tool equipped with solid theoretical basis, and produces results with identical format to standard ERP, thus facilitating all subsequent analyses. The improvement of ERP dynamic waveform by ReSync may contribute to future research on complex brain cognitive dynamics. Many open issues still remain, below I discussed some of them.

When/why should I use ReSync and how would ReSync benefit my research?

This article focuses on presenting the theoretical and methodological framework of the method ReSync. Its utility and potentials remain to be further revealed by future applications. In principle, ERPs should always be jitter-corrected. The question is *whether the correction is correct*. Jitter correction methods may arbitrarily or over ‘correct’ the ERP, resulting an estimation of neural response pattern that is worse than standard average ERP (although blurred by jitter). This issue is related to many factors, such as whether the jitter is substantially present in the data or not, or whether the timing can be reliably obtained or not. A systematic investigation of this issue based on simulation data is necessary. More importantly, the simulation studies should be reference-able in real data analyses. In this regard, I identified two key signal features that may crucially determine the necessity of jitter correction: signal-to-noise ratio and degree of latency variability. The two factors have been quantified as universally reference-able measures, SNR and RLV (see Method). In general, if SNR and RLV are low, it is less needed to correct the jitter as the correction method would more likely to produce error, vice versa. Based on simulation, I drew a parameter sweeping map of SNR and RLV showing a definite boundary across which ReSync-ed ERP is either better or worse than standard average ERP (Fig 9d). This parameter map could serve as a reference for real data application as both SNR and RLV are unit-less and can be directly calculated in real EEG data. I exemplified two datasets in terms of where the individual ERP components fall onto the parameter map. The results showed that a significant number of participants (especially the firs dataset) fall onto the region where jitter corrected is recommended.

Using the SNR-RLV map is a very straightforward way to make an initial judgement on whether it is worthwhile to apply ReSync to correct the ERP. Due to the nature of some experimental investigation (e.g., looking at very subtle neurocognitive process, or neural response activity in natural scenes), the SNR-RLV value may fall far out of the recommended region (Fig 9d). In those situations, standard ERP is simpler, safer, and better, unless a more advanced jitter-correction approach is demonstrated to be better in handling noise in the future. It has to be also noted here that, when judging whether ReSync is worthwhile by calculating SNR and RLV and mapping to the SNR-RLV map, it is suggested to select the prominent electrode(s) (where the activation is strongest), for example, parietal areas (Cz, CPz, Pz, depending on the specific dataset) for P3 component, occipital areas (e.g., PO7/8, O1/2) for early P1/N1 complex. Once the most prominent electrode(s) is designated for best representing the component of interest, ReSync will work on estimating its single trial latencies from there, and all the other electrodes on the entire scalp will be jitter-corrected based on the estimated latency variability from only the prominent electrode(s). Procedure and scripts can be found in the toolbox manual.

Individually specific application of ReSync

A straightforward application of ReSync is to determine the electrode(s) and time window(s) of where the components need to be jitter-corrected. The determination of the parameters can be based on the pattern of grand average ERP, and then be universally applied to each individual. This may be a sub-optimal procedure, considering the existence of substantial individual differences in ERP pattern. For example, one participant may have a P3 complex covering from around 200 ms to 500 ms, another covers 300 ms to 800 ms, yet another may simply show a flat P3 (low SNR). Same thing applies on scalp distribution: some participants' P3s center at Cz, others' center at CPz or Pz. Therefore, individualized determination of ReSync parameter is, in principle, desirable. However, individualized parameter determination also faces several issues. First, it may be difficult to determine the idiosyncratic cases where the

ERP components are poorly shown (e.g., flat P3). One option is to simply skip ReSyncing those idiosyncratic individuals (e.g., with low SNR, see the evaluation section above), which has to be done for all conditions for that participant (if ReSyncing is only done in one condition, this may create spurious between-condition effects). Second, individualized parameter setting is laborious and hard to automatized, which compromises reproduction. Development in this line is highly desirable.

Going to the source

The ReSync algorithm is essentially for processing a time series with embedded event markers and re-synchronizing the event-elicited components from event to event (trial to trial), with respect to the event onset. With that being said, the method can be directly applied to neural source activities that are derived from source reconstruction algorithms. At the sensor level, the time series that is fed to Resync is the EEG trace from a single electrode (or average from a few electrode). Similarly, for applications on source level, the time series is just the neural source activity that are constructed from source algorithms. For example, one can apply ICA to the scalp EEG and obtain source activity traces as many as the electrodes. Each source trace can be treated as an 'electrode' to be fed into ReSync for jitter correction of the source ERP. Similarly, time window should be specified, which can be guided by the pattern of source ERP. One potential advantage of source-level analysis is that the reconstructed source activity may be more specific in capturing some functionally distinct neural activities, such as, P3, N400, or early perceptual components, that are somehow better isolated from neural noise or other activities than that in sensors. And ReSyncing the source activities is a step that further improves the representation of neural response activities in the brain. The instruction on how to apply ReSync on a general time series (e.g., source activity) is provided in the online manual.

Summary

In this paper I presented an easy-to-use, very straightforward method for correcting the latency jitter in ERP data – a problem that theoretically exists in all ERP datasets. I reviewed the major previous methods that directly or indirectly dealt with the ERP latency jitter issue, and presented the novelties and uniqueness of the ReSync method, followed by validations and evaluations in both simulated and empirical EEG data. The novelties and uniqueness can be concisely summarized below: 1) ReSync produces a jitter-corrected version of ERP data that are in exact the same format as standard ERP, thus allowing for application of all existing ERP analysis methods and paradigms to the jitter-corrected version. 2) ReSync evaluates the two key parameters in ERP data, namely SNR and RLV, to help determine whether the data quality and feature are suitable for the ReSync-based jitter correction or not. The judgement can be very straightforwardly made by locating the SNR-RLV to the parameter map indicating whether ReSyncing is better than standard ERP or not. The indicator is provided in the toolbox. 3) ReSync *automatically* determines the dominant frequency in the single trial ERPs, thus allowing for a more precise capturing of the phase-locked component (event-evoked component) and determination of its single trial latencies by effectively excluding the distraction of high frequency noise component. It is hoped that the ReSync jitter-correction toolbox can contribute to the brain research in the aspect of characterizing the neural response patterns.

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