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Single trial analysis of field potentials in perception, learning and memory

Hernan Gonzalo Rey, Maryam Ahmadi and Rodrigo Quian Quiroga

The analysis of single trial responses of field potentials is an important tool to study brain signals. Single trial analyses can indeed provide additional information that is obscured or simply not available in the average responses. The importance of studying single trial responses is reinforced by the fact that different brain processes are correlated with trial-by-trial variation of the responses. Here, we review key studies implementing single trial analyses of field potentials — using methods such as single trial latency, amplitude and power changes, spike and LFP relationships, correlations between areas, cross frequency coupling, decoding of the presented stimuli — that bring light into the neural basis of perception, learning and memory.

Addresses
Centre for Systems Neuroscience, University of Leicester, Leicester LE1 7QR, UK

Corresponding author: Quian Quiroga, Rodrigo (rqqg1@le.ac.uk)

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Introduction

Brain electric potentials (EEG, ECoG or LFPs) can be measured extracellularly with respect to a reference [1,2]. Responses of field potentials triggered by the presentation of a stimulus have typically relatively small amplitude compared to the background brain activity. It is therefore hard to identify such responses from single presentations of the stimulus and a standard approach is to average several presentations, so that the ongoing activity cancels out, leaving the so-called Event Related Potential (ERP). But the main limitation of ensemble averaging is that it implies a loss of information related to trial-by-trial changes. These changes could be systematic — such as a decrease in amplitude or latency with trial number that could be related to learning or memory processes — or unsystematic — for example, a trial-to-trial variability that correlates with perceptual performance [3].

In the current review we briefly present the most common techniques for performing single trial analyses of field responses, and we then describe recent studies using this approach that reveal important information about perception, learning and memory processes.

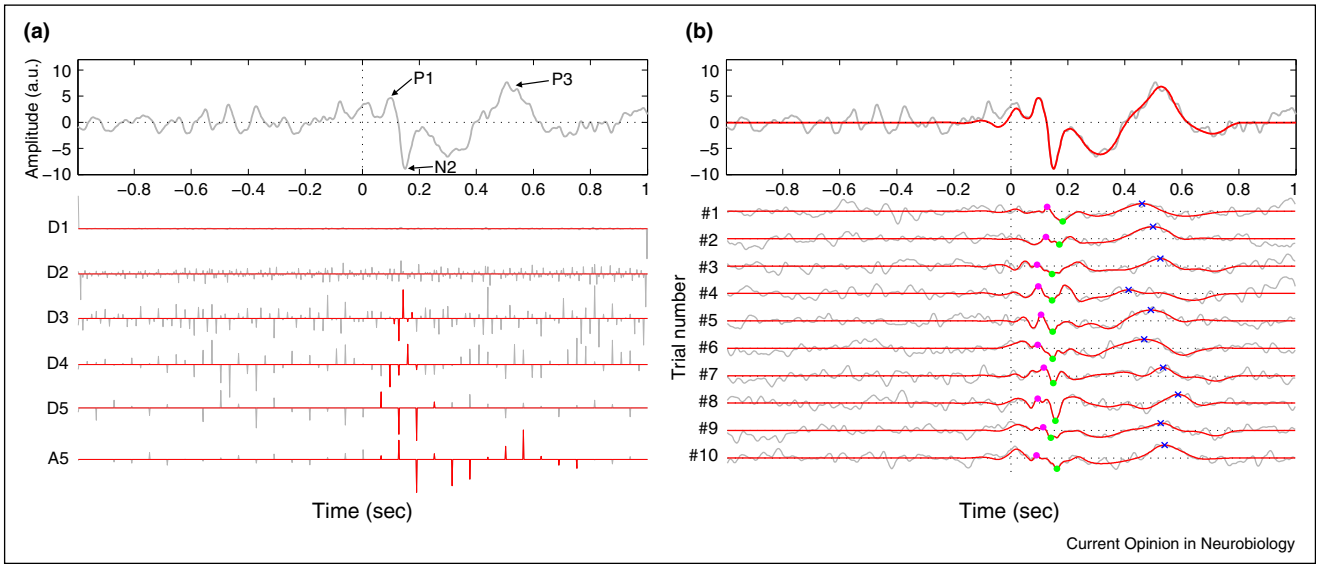
Basics of single trial analyses

A time–frequency decomposition of the field potentials can be obtained using the wavelet transform, which is the convolution of a signal with a single wavelet function localized at different times and with different sizes [4]. Each wavelet coefficient represents the activity of the signal at a particular time and frequency range, offering an ideal representation of time varying patterns in the ERPs. For example, in Figure 1a we show the average ERP obtained with a visual oddball paradigm, where we observe three components (P1, N2 and P3) that are correlated with coefficients at different scales (marked in red).

A first strategy to perform a single trial analysis is to identify the ERPs in the single trials and then evaluate, for example, single trial latency and amplitude changes. For this, an automatic method has been recently proposed, which basically identifies the wavelet coefficients correlated with the average evoked responses and then reconstructs denoised single-trial traces using only these coefficients [5] (see Figure 1b).

Another approach to perform single-trial analyses is to define an instantaneous phase and then evaluate if there is a preferred phase at which the neurons fire, or a trial-by-trial correlation between the phases at different recording sites, or a concentration of phase values across trials after the presentation of a stimulus, or a correlation between the phase and the amplitude at different frequencies. Two methods have been proposed to define an instantaneous phase (and have been shown to give the same results [6]): the Hilbert transform and the wavelet transform, in the latter case using a complex (Morlet) mother wavelet. The basic idea is that both transforms give a complex representation of the signal from which it is possible to define an instantaneous phase (and amplitude). The assessment of trial-by-trial correlations between phases allows also the quantification of 'phase

Figure 1



Wavelet decomposition and denoising. **(a)** Top panel: the average visual evoked potential (VEP) recorded at O2 in a typical subject during an oddball task shows three components (P1, N2 and P3). Bottom panel: the dyadic wavelet transform was implemented using an efficient and fast hierarchical algorithm, named 'multiresolution decomposition', which decomposes the signal at different detail levels and a final coarse approximation. In this case, a five scale wavelet decomposition (grey) of the average VEP was used. D1–D5 are the decomposition details and A5 is the last approximation (the lowest frequency band of the signal). Each coefficient represents the activity of the signal at a specific time and frequency band. In each scale, the coefficients chosen for denoising are shown in red. **(b)** Top panel: original (grey) and denoised (red) average VEPs. Bottom panel: ten original (grey) and denoised (red) single trial responses, with the corresponding peak identifications for each ERP component.
Adapted from [5].

synchronization' between different recordings sites. Alternatively, single-trial correlations between recording sites have been also established using coherence, which gives a measure of correlation as a function of frequency.

Yet another approach to single-trial analyses is to predict on a trial-by-trial basis the stimulus eliciting a particular response using decoding algorithms, and eventually evaluate which features of the response contain information about the stimulus [7].

Single trial studies of perception

The study of single-trial correlations between LFPs and neuronal firing has received increased attention in recent years. In particular, it has been shown that sensory areas can carry information about a perceived stimulus not only in the spike count but also in the LFP phase of firing, that is, the phase of the single trial LFP at the time of the spikes [8,9]. These works demonstrated that the phase of firing enabled discerning between stimuli that could not be distinguished on the basis of spike counts alone. Similarly, evidence for an 'LFP phase code' has been reported in the prefrontal cortex [10,11] of rats and macaques, and the superior temporal sulcus (STS) of macaques [12].

The specific phases of oscillations at a given trial have been also shown to be correlated with perception. The phase in the theta (4–8 Hz) and alpha (8–13 Hz) EEG shortly before stimulus onset was enough to predict the detection of a brief flash presented at the threshold of conscious perception [13]. In line with this finding, a critical role of the pre-stimulus alpha phase in visual awareness was confirmed using a masking paradigm, in which the appearance of a target at a particular alpha phase led to a suppression of cortical activation after stimulus onset and a decrease in the likelihood of target detection [14]. Moreover, repetitive transcranial magnetic stimulation in the posterior parietal cortex within the alpha frequency range (10 Hz) successfully entrained the phase of alpha oscillatory activity and produced a phase-dependent change on subsequent visual perception [15•]. A similar effect was also found during a tactile perception task [16], suggesting a common mechanism taking place across different sensory modalities, with alpha oscillations shaping the state of brain activity necessary for conscious perception.

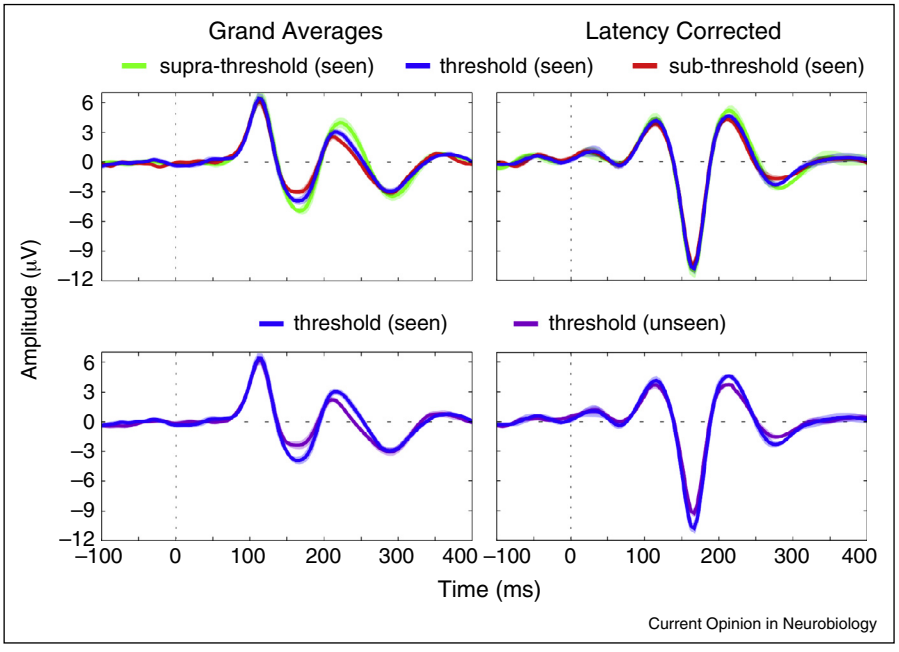
Single trial analyses are particularly important to study high frequency activity because small latency jitters across trials tend to cancel out the average responses. Beta (13–30 Hz) and gamma (30–80 Hz) oscillations have been observed in response to stimulation across different modalities [17], and have been proposed to be critical for merging activity of groups of neurons and brain areas into unified percepts [18]. For example, latency correlations across neuron pairs in primary visual cortex have been

observed during high gamma activity [19]. Furthermore, a recent study with simultaneous recordings from macaque V1 and V2 showed that gamma frequency increased in both areas with the contrast of grating stimuli and it fluctuated by ~15 Hz during constant contrast stimulation [20]. Interestingly, these fluctuations were highly correlated on a trial-by-trial basis in both areas, supporting the idea of gamma coherence as an effective means of communication [57]. In addition, it has been reported a communication between areas through cross frequency coupling between theta and gamma, which was proposed to coordinate activity in distributed cortical areas [21,22].

ECoG and EEG studies in humans have also shown that single trial analyses can be very helpful. In particular, it was shown that it is possible to decode the object category (e.g., faces, animals, vehicles, etc.) using ECoG recordings from visual cortex as early as 100 ms after stimulus onset [23]. Moreover, voltage topographies in EEG were also used to decode sound category (living or man-made) even when the subjects could not consciously perceive such categorization [24]. At the same time, category selective ECoG electrodes showed an increase in single trial gamma power occurring together with evoked responses specifically associated with successful recognition [25]. Functionally relevant increases in single-trial gamma power have been also correlated to the subjective perception by the subjects and were enhanced by selective attention [26].

Given the importance of face recognition for our behavior and social interaction, a large number of studies have focused on studying the perception of faces. Using scalp EEG recordings, it was reported that the perception of 'Mooney' faces gave rise to trial-by-trial phase synchronization between distant EEG sites in the gamma band [27]. Furthermore, the N170 ERP component has been shown to differentially mark the perception of faces against other type of visual stimuli [28]. By concurrently using EEG and fMRI it was shown that the perception of upright faces correlated with larger single trial N170 amplitudes, which in turn were correlated with fMRI activations in the STS [29]. Additionally, a recent study using backward masking [30••] showed that the average N170 was modulated both by the noise level of the image and by the subjective perception of the face by the subjects (Figure 2). However, a single trial analysis revealed that, whereas the N170 differences with noise level vanished in the latency corrected averages (LCA) — that is, the averages obtained after identifying and aligning the single trial N170 latencies — the difference between the seen and unseen trials remained. Thus, on the one hand, the modulation obtained for the different noise levels was due to a latency variability across trials, and on the other hand, the modulation with conscious perception was due to an increase in the single trial responses upon recognition of the faces. Interestingly, this study also showed that it was possible to decode the

Figure 2



Analysis of the N170 response measured in electrode PO8. Average N170 responses for varying noise levels (threshold, subthreshold, and suprathreshold) and separated according to recognition (left plots). In the first case, but not in the second one, the differences in the average responses disappeared after latency correction (right plots). Shaded area around mean values denotes SEM.
Adapted from [30••].

subjects' perceptual decisions (seen or unseen) based on the single trial amplitude of the N170, but not using the amplitude of other (P1, P2) ERP components.

Single trial studies of learning and memory

Single trial analyses are particularly suited to study processes such as learning and memory, where changes in neural responses take place even within a single recording session. For example, a study of auditory evoked potentials in rats described six components in the average ERPs [31]. Interestingly, a single trial analysis of the denoised responses showed different rates of habituation (a decrease in the neural response upon repeated presentation of a stimulus) and sensitization (increased response after the first stimulus presentation) for different components. This revealed the fact that different ERP components were correlated with different functions, something that could not be inferred from the average ERPs.

In another study, two groups of subjects learnt to respond accurately to the appearance of a slightly different infrequent sound in an auditory oddball paradigm, generating a mismatch negativity component (MMN) [32]. The first group of subjects was sleep deprived on the night after learning the paradigm and they showed a decreased post-training MMN compared to the second group of control subjects. Then, it was argued that consolidation during sleep elicits a recruitment of a larger population of neurons or an increase in synchronization. However, a single trial analysis demonstrated that the MMN enhancement in the control group stemmed from a reduction in the MMN latency jitter, as the differences disappeared after performing LCAs. Therefore, rather than changes in the size of the responses, consolidation during sleep led to a more precise response onset.

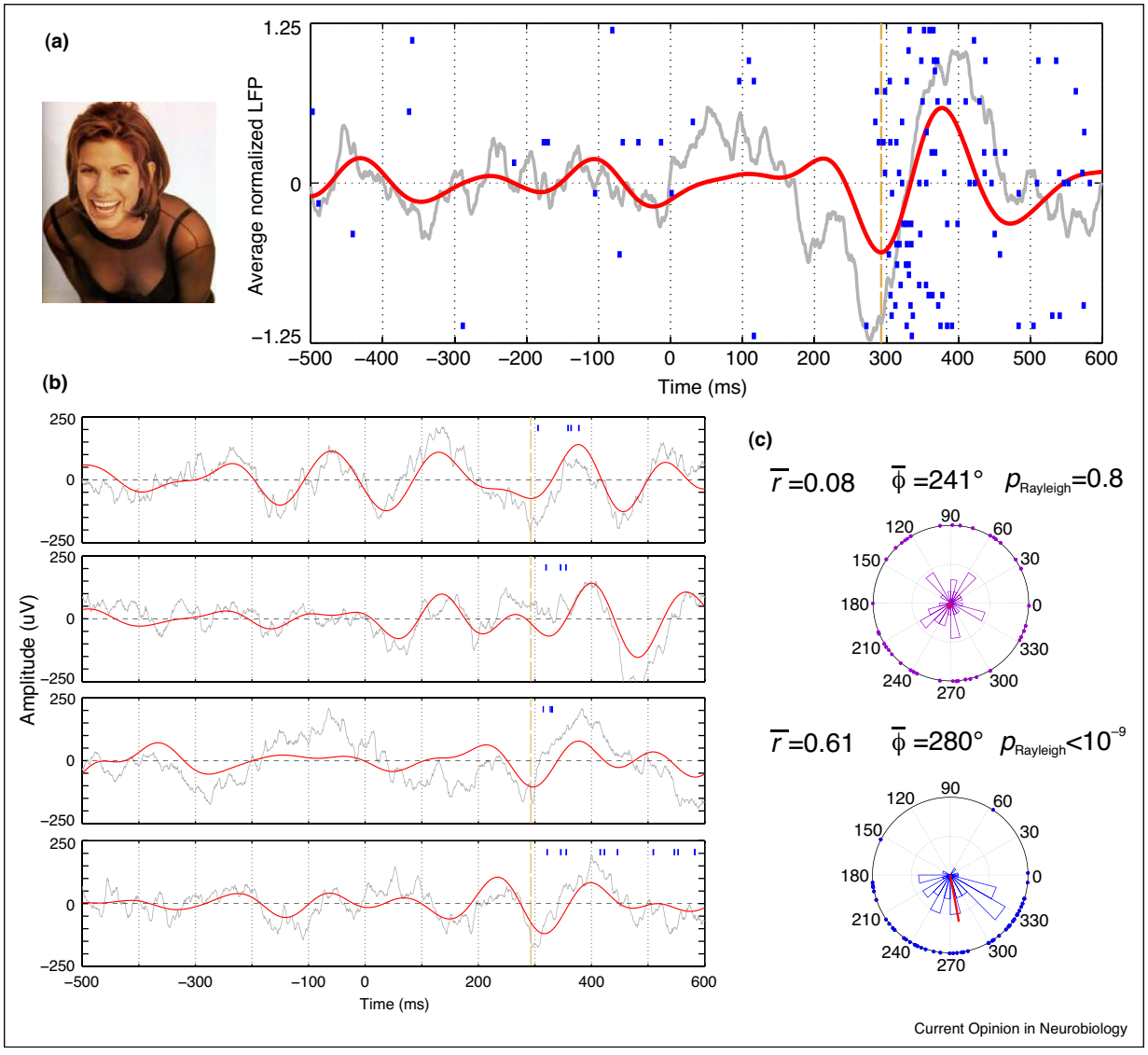
The role of oscillations in learning and memory has been well documented [17,22,33]. In a four-arm-radial maze, where rats had to choose one arm for reward, an increase in single trial theta power in CA1 was observed during the decision making epoch [34] being higher preceding correct than incorrect trials. Furthermore, recordings from the CA3 region of the rat hippocampus showed an increase in theta–gamma coupling while the animals learned an item-context association task, and the strength of this coupling was correlated with an increase in performance accuracy during learning [35]. Such increase in coupling has also been reported in the rat CA1 [36••], where, in addition, an increase of the coherence in the gamma band between lateral entorhinal cortex (EC) and CA1 was correlated with the learning of an association task. Moreover, theta–gamma coupling changes in the rat orbitofrontal cortex correlated with the learning of an odor discrimination task [37].

Several studies have analyzed field potentials during the encoding phase of a memory task to predict the performance during the recall phase. Particularly, theta–gamma coupling in the rat hippocampus has been correlated to the recall of stored information [35]. Furthermore, successful encoding of visual stimuli was correlated with an increase in single trial theta power in frontal cortex, of gamma power in posterior cortex, and the coupling between them [38]. Such an increase in theta and gamma power was also reported with ECoG in humans while participants recalled lists of common nouns [39], and with magnetoencephalography (MEG) during a declarative memory task [40]. A simultaneous EEG/fMRI study [41] showed that the single-trial theta power also predicted memory performance while being correlated with patterns of voxel activations.

The medial temporal lobe (MTL), a region of the brain comprising the hippocampus, the EC, the amygdala and the parahippocampal cortex, has a critical role in declarative memory [42]. Prestimulus theta MEG activity in the MTL was correlated with performance during free recall of a list of words [43]. A similar effect was found using EEG, with recall performance correlating with differences in the amplitude of ERPs recorded in the rhinal cortex and the hippocampus [44]. In addition, the phase of the LFP recorded from the human MTL was used to decode correct/incorrect choices in a memory 'card-matching task' [45]. Furthermore, by simultaneously recording LFPs and spiking activity, it was shown that successful memory formation in humans is predicted by a tight coordination of spike timing with the local theta oscillation during encoding [46].

In the human MTL it has been shown the existence of neurons with selective and invariant responses that represent the meaning of the stimulus for declarative memory functions [47,48]. In [49] it was shown that combining the single trial spiking and LFP activity enhanced the predictions of the presented stimuli in comparison with the accuracy obtained with each signal alone. In another study, several pictures were presented for a short time, so in some trials they were recognized and in others they were not [50••]. Figure 3a shows an exemplary response of this study, representative of the findings in the whole population: the average ERP exhibits a large deflection prior to the onset of the spiking response, only for the recognized trials; the neuron tended to fire at a particular phase of the LFP response (Figure 3b), as quantified by a 'phase locking factor' (i.e., the consistency of the LFP phases at the time of the spikes) shown in Figure 3c. From this, it was argued that the theta activity provides a temporal window for triggering the single neurons' firing in the MTL upon picture recognition. Besides the difference in the theta average power between recognized and non-recognized trials, there was also larger single trial power activation in the high gamma band for the recognized trials (Figure 4), related to the selective activation of neurons representing a particular concept.

Figure 3

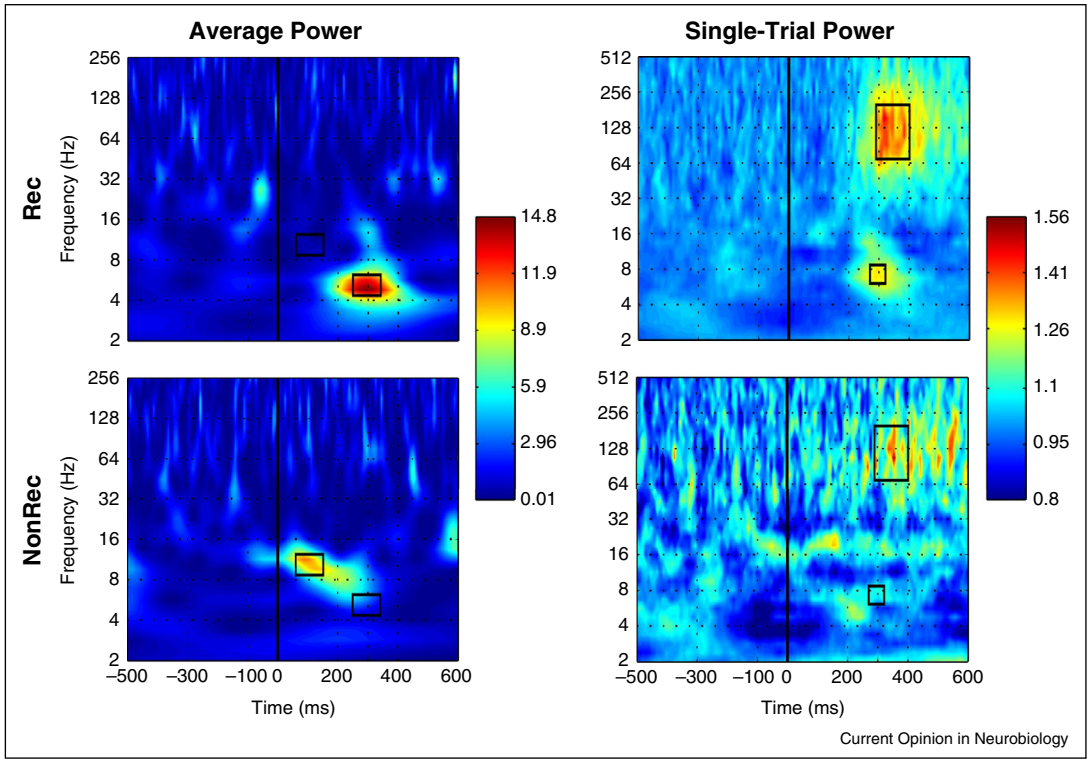


Spikes and LFP responses in the human medial temporal lobe. **(a)** Example of a neuron in the left anterior hippocampus that responded to a picture of Sandra Bullock. The raster plot, onset of the spiking response (dashed vertical line), raw average LFP (grey), and average LFP in the theta band (4–8 Hz; red) are shown. Only the 31 recognized trials were used for computing firing rate and average LFP. **(b)** Four exemplary single trials showing the raw and theta LFPs and the spike occurrences. In all the cases the beginning of the spiking response takes place during the rising phase of the LFP. **(c)** Histograms of the LFP theta phase at the time of the spikes, showing a large difference before (top) and after (bottom) stimulus presentation. $\bar{r}$ and $\bar{\phi}$ represent the magnitude and angle of the mean phase vector, whereas $p_{Rayleigh}$ stands for the p-value of a Rayleigh test for non-uniformity of circular data.
Adapted from [50••].

Interestingly, these human MTL neurons share many features with place cells (neurons that fire when the animal passes through specific locations) in the rodent hippocampus [47]. The firing of place cells is correlated with the phase of the theta LFP and such phase coding has been shown to provide information beyond the one given by the firing rate alone [51]. Although the selective tuning exhibited by place cells is not seen in the LFPs at a single anatomical site, a recent study showed that the spatiotemporal structure of the theta rhythm can encode position as robustly as neuronal spiking populations, leading to a distributed LFP code [52•].

A well-established relationship between the spiking and LFP activity in the rat hippocampus is called 'theta phase precession', namely the advanced firing of a place cell at consecutive theta cycles as the rat crosses the associated place field [51]. Place cells can also fire in temporal

Figure 4



Recognition effects on average and single trial LFP power in the human MTL. Left: time–frequency plot of the average LFP power for recognized (rec) and non-recognized (nonrec) picture presentations [50••]. The regions of interest (ROI) used for statistical comparisons are indicated by black rectangles. There is a significant increase in the theta band for rec trials and in the alpha band for nonrec trials. Right: time–frequency plot of the single-trial LFPs power for the rec and nonrec trials. There is a significant increase in theta and gamma bands for rec trials, but not for nonrec trials. The plots are the grand average across all significant responses.
Adapted from [50••].

sequences during an individual theta cycle [22]. In particular, a study comparing rats experiencing passive forward and backward traveling on a model train revealed that, whereas the firing fields of place cells remained stable, the order in which they were activated within the theta cycle was reversed [53••]. A sequential firing of hippocampal cells was also found during a preplay of the locations to be visited by the rat (also showing phase precession) [54] and in head-fixed and immobile rats while they remembered odor stimuli across a delay period [55•] (with the firing appearing during a strong ongoing theta rhythm). In addition, sequential activation of place cells during replay and preplay were shown to be triggered by sharp waves in the LFPs [56].

Conclusions

In this review we described studies using single trial analysis that shed light into our understanding of the neural basis underlying perception, learning, and memory. Among these studies, we showed how the prestimulus phase or single-trial modulations of gamma activity were correlated with processes such as conscious perception or the prediction of recall performance. Moreover, single-trial field potentials can also be correlated with the firing of neurons, which allows comparing and correlating information from the microscopic and mesoscopic levels. In particular, we showed examples of preferential LFP phases of neuronal firing that correlated with conscious perception or recall. Altogether, we argue that single trial analyses offer information way beyond the one available in classic ensemble averages. The use of single trial information in fact encourages a paradigm shift where trial-by-trial variations, and their potential correlations with sensory and cognitive processes, are not avoided (to obtain better averages) but sought.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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