



Review article

Entrainment and synchronization of brain oscillations to auditory stimulations

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ABSTRACT

Oscillations of neural excitability shape sensory, motor or cognitive processes. Furthermore, a large body of research demonstrates that intrinsic oscillations are entrained by external rhythms, allowing a simple and efficient way to enhance human brain functions. As an external stimulation source, repeating acoustic stimuli have been shown to provide a possible pacing signal for modulating the electrical activity recorded by the electroencephalogram (EEG). In this review, we discuss recent advances in understanding how rhythmic auditory stimulation can selectively modulate EEG oscillations. Despite growing evidence, recent evidence suggests that standard methods of data analysis are often insufficient for a definite proof of entrainment in some instances. In particular, we stressed that the complexity of the elicited modulations, often varying in phase and frequency on a short timescale, requires time-frequency measures that are better appropriate to analyze driven brain phenomena. Once entrainment is clearly established, one can assess the specificity of its expression, thus providing a better understanding of the physiology underlying brain modulation and a faster translation to treatment programs in various psychopathologic conditions.

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Network oscillation represents rhythmic changes in excitability of neuronal populations over a wide range of frequencies from 0.01 to over 200 Hz (Buzsáki and Draguhn, 2004). During a brain oscillation, a single neuron is not equally likely to discharge at all points of time. Instead, in response to these rhythmic changes in excitability, its likelihood of discharging is modulated by local extracellular and membrane potentials that, in turn, are reflected by the phase

of the network rhythm. As a result, the high excitability part of the oscillatory cycle might act as a “window of integration” and stimuli falling within one high excitability phase become united to form the percept of one integrated item (Varela et al., 1981; Fries et al., 2007). Owing to their spatial and temporal integration, oscillations have been proposed to play crucial roles for facilitating functional connectivity between anatomically distributed brain regions and grouping local neural information to serve a variety of sensory, motor, and cognitive functions (Varela et al., 2001; Fries, 2005; Uhlhaas and Singer, 2010).

Critically, there are indications that a direct manipulation of brain oscillatory activity is possible through repetitive sensory

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stimulations. The idea of modulating oscillatory rhythms via rhythmic stimuli to modulate cognitive performance is not new (Adrian and Matthews, 1934). Indeed, this approach is built on the long-standing observation that when a sensory stimulus is repeated at a fixed rate, it generates a periodic change in voltage amplitude in the electrical activity recorded by the electroencephalogram (EEG). Based on this old idea, exciting new lines of research demonstrated that the enhancement of different phases of EEG oscillations with something as simple as repeating acoustic stimuli can enhance cognitive functions like memory or learning. For example, as discussed latter in this review, 40 Hz acoustic stimulation improve memory in a mouse model of Alzheimer's disease (Iaccarino et al., 2016; Lee et al., 2018; Martorell et al., 2019). Furthermore, simple acoustic stimuli like pink noise clicks can be used to drive sleep slow-wave activity, producing benefits to deep sleep and memory consolidation in humans (Ngo et al., 2013). In this context, an increasing number of researchers began to realize that neural entrainment to auditory stimulation may constitute a unique gateway to modulate human brain function.

This review highlights recent advances in understanding how periodic auditory stimulations can selectively modulate brain oscillations. We stress that the complexity of the elicited modulations, often inducing subtle phase changes on a comparatively fine timescale, requires careful attention to more sophisticated methods of data analysis. For this purpose, time-frequency measures are well suited to analyze driven brain oscillations. These relatively new measures of dynamic brain processes have exquisite temporal resolution and allow the study of neural networks underlying sensory and cognitive events, thus providing a better understanding of the physiology underlying brain entrainment.

1. The many faces of the brain oscillations

In humans, large-scale oscillations can easily be recorded with the EEG when the subject is at rest or at the time of specific event-related brain potentials during cognitive tasks. According to the classification of Galambos (1992), different types of oscillatory activity can be distinguished: *Resting state oscillations* refer to those generated while the subject is not engaged in any experimental task. For example, scalp recorded EEGs provided initial evidence that during wakeful rest the brain exhibits a posterior dominant 8–12 Hz oscillation, i.e. the alpha rhythm (Berger, 1929). Nevertheless, neural activity is continuously modulated even during sleep. In particular, environmental stimuli, reaching the brain through the senses, activate or inhibit neuronal populations and modulate ongoing activity. In this respect, *evoked oscillations* are phase-locked responses (i.e., synchronized in time) to an individual stimulus, whereas *induced oscillations* are responses that are reliably elicited by a stimulus but are not time-locked to it. Evoked oscillations usually occur earlier than induced oscillations and represent bottom-up sensory processing, whereas induced oscillations reflect higher-order cognitive processing (Tallon-Baudry et al., 1996). In particular, evoked gamma oscillations (40–120 Hz) may reflect the local coordination of neuronal firing mediated by high-frequency oscillations in post-synaptic potentials (Hasenstaub et al., 2005). In contrast, slower oscillations (< 20 Hz) facilitate coordinated activity across longer distances between remote regions or between hemispheres, which can involve longer, poly-synaptic conduction delays of tens of milliseconds (Varela et al., 2001). Finally, *entrained oscillations*, or steady-state evoked potentials (SSEP), are elicited by repetitive auditory or visual stimuli presented at a fixed frequency. Interestingly, the SSEP reveals resonance frequencies that resemble those frequencies of spontaneous oscillations in the EEG (Herrmann, 2001; Hanslmayr et al., 2019). This similarity with individual resting oscillation frequency suggests that rhythmic stimulation recruited intrinsic network

oscillations, rather than creating oscillations de novo. Therefore, SSEPs may probe the brain's ability to generate endogenous oscillations that are entrained or synchronized with the frequency of the external stimulus. Nevertheless, it is plausible to think that evoked, induced, and entrained oscillations may reflect different neuronal processes and mechanisms (David et al., 2006).

Furthermore, it is likely that these different types of oscillatory activity contribute to different physiological functions depending on where in the brain and with what neurophysiologic parameters (amplitude, frequency, phase, coherence) they occur.

2. Time-frequency structures of dynamic oscillations

In principle, every signal can be decomposed into sinusoidal oscillations of different amplitudes and frequencies. Such decomposition is usually computed using the Fourier transform to quantify the oscillations that constitute the signal. Nevertheless, the mere presence of power in a given frequency band does not necessarily imply the presence of an oscillation at that frequency. For example, broad-band transients in the EEG signals, such as evoked potentials or muscle and eye-movement artefacts will yield power in multiple frequency bands, without any oscillations being present. Because the filtering process may contaminate the data with spurious oscillations, several methods were proposed to avoid it by estimating the whole spectral characteristics of the signal through the computation of the time-frequency transform (Le Van Quyen and Bragin, 2007). Furthermore, the frequency content of a signal may change over time or oscillations could be only present during small parts of the recording, which will lead to a broadening of the power spectrum. Here Fourier analysis (highly dependent on the stationarity of the measured signal) are not suitable to identify these changes.

Time-frequency decompositions like the Wavelet analysis attempt to solve these problems by decomposing a time series into a time-frequency domain simultaneously. For instance, using wavelet analysis it is possible to obtain information on both the amplitude and phase of any oscillatory signal within the series, and how these amplitudes and phases vary with time. Typically, Morlet wavelets are recommended as they provide an ideal compromise between time and frequency resolution (Fig. 1A) (Le Van Quyen and Bragin, 2007). Wavelet transformation can then visualize the result compactly, usually in a 2D color image, a so-called time-frequency representation (or "TF-plot"). As seen in the Fig. 1A, oscillations present a bubble-like shape in the time-frequency representation and appear as isolated islands in a specific frequency band. Applied to scalp EEG, a good indication of the existence of oscillatory activity in a TF plot is the presence of a narrow-band power increase that last for at least one or two (for low frequencies) or more (for high frequencies) periods of the oscillation (e.g., 400 ms for a 5-Hz oscillation, or 100–200 ms for a 40-Hz oscillation). Short-lasting broadband EEG responses (e.g. a 40–100 Hz increase in power that lasts only for a few tens of ms) are usually indicative of the presence of muscle artefacts or stimulus-related transients.

In order to estimate the evoked, induced and/or steady-state response in the EEG to a specific rhythmic stimulation pattern, the time-frequency power is computed for each single trial independently and then averaged across trials yielding TF maps of both stimulus-evoked and-induced activities (Fig. 1B). Evoked oscillations are phase locked to the stimulus, whereas induced oscillations are not. Operationally, these two phenomena are revealed by means of trial averaging and spectral analysis respectively. Evoked responses are characterized as the TF map of the average. To estimate induced oscillations, the TF decomposition is applied to each trial and the ensuing power is averaged across trials. Induced responses are the average power that cannot be explained by the power of the average. Obviously, each of the approaches

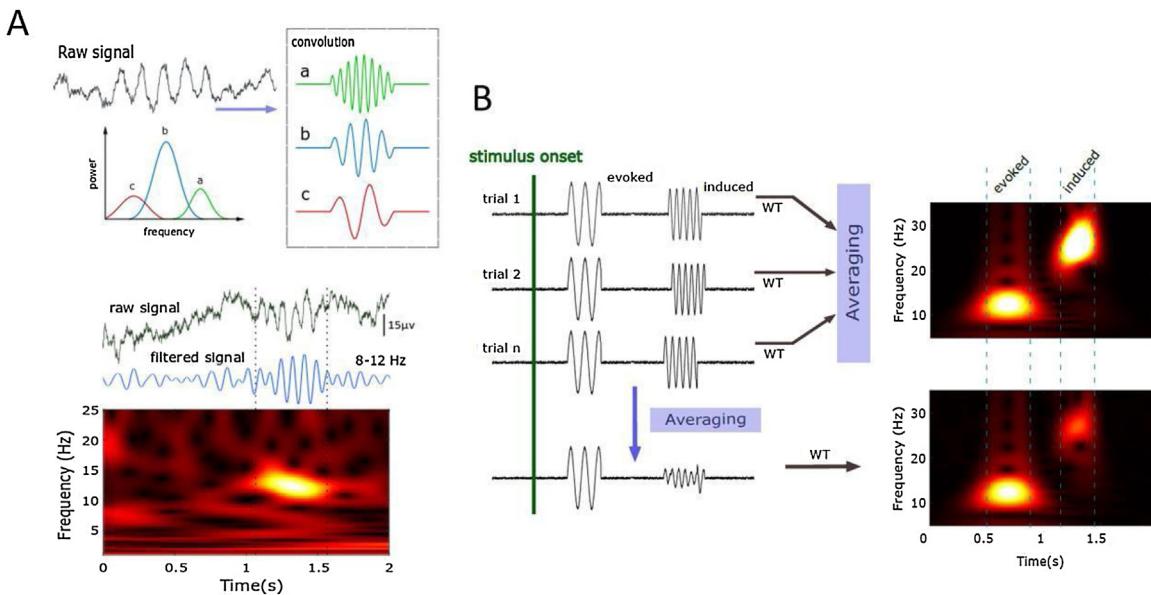


Fig. 1. Wavelet analysis and time-frequency representations.

A. Wavelet transform allows a time-frequency decomposition through the convolution of the raw signal with wavelets of different frequencies. The frequency components of the oscillations can be seen in the TF representation as well-defined bubbles in a specific frequency band (here around 12 Hz for the selected EEG signal). **B.** The order of trial averaging and spectral analysis is different for evoked and induced responses. Time-locked trials (evoked activities) could be averaged before performing the Wavelet transform. On the other hand, induced activities have a jittering behavior and it is necessary to obtain first the Wavelet power before performing trial averaging.

listed above also needs to be associated with appropriate statistics (Nichols et al. 2001). Standard parametric tests are sometimes sufficient: for example, time-frequency domain properties can be directly compared between two groups of trials corresponding to two distinct behavioral outcomes, using a Student's *t*-test – the null hypothesis being that the pre-stimulus means for the two conditions are equivalent at each point in time. Reviews and comparison of these methods including thoughtful discussion on the correct interpretation of them can be found in several papers (Nichols and Holmes, 2001; Pernet et al., 2015; Groppe et al., 2011).

Despite the advantages of time-frequency decompositions in the analysis of brain oscillations, common systematic errors can arise when computing the resulting potential. As the evoked and induced oscillations are time associated activities, a precise synchronization triggering signal is required between the ongoing EEG activity and the stimulus onset. In the absence of this precise synchronization, even a little jittering between the times of stimulus onsets among consecutive trials could lead to a diminished resulting potential. In addition, as the induced potentials present an inherent jittering in frequency among stimuli, their corresponding TF representation could be characterized by a wide bubble, not very well localized at one particular frequency, but rather within a frequency range (Fig. 1B).

3. Phase-locking signatures of neural entrainment

If a rhythmic stimulus is presented, a brain response can be measured that follows the temporal structure of the stimulus. These steady-state evoked potentials in response to sensory stimuli were first reported by Adrian and Matthews (1934) in a remarkable article. The authors recorded the EEG from the occipital lobe while subjects were exposed to flickering light with frequencies up to 25 Hz. When the flicker frequency was adjusted to the individual alpha frequency "... the waves may become extremely regular and may continue for many minutes without the usual waxing and waning in size" (p.

380). In this case, neuronal entrainment is characterized by an increase in signal amplitude (or power) at the stimulus fre-

quency as more and more neurons become phase aligned to the entraining stimulus. But, if the stimulation frequency matches the frequency of an endogenous oscillatory activity, one would not necessarily expect an increase in power at this frequency, but rather a simple increase in phase-locking between recorded EEG signal and presented stimulus that develops over time (green curve in Fig. 2-A) (Thut et al., 2011; Notbohm et al., 2016; Hanslmayr et al., 2019). In this case, phase resetting refers to the modulation of the phase of ongoing oscillations by external event-related input (Fig. 2-B). Because it is influenced by amplitude, analyses merely based on averaged TF energy distributions cannot detect this phenomenon. Here, tools in which the phase component could be obtained separately from the amplitude are necessary. Using a wavelet decomposition for phase extraction, for example, synchronization between periodic stimuli and EEG responses can be analyzed with the so-called "stimulus-locked inter-trial coherence" (ITC). The ITC reflects the temporal and spectral synchronization within EEG and captures the consistency in phase alignment of neuronal activity that is elicited by task events. Following Makeig et al. (2002), ITC can be computed with following formula:

$$ITC(t, f) = \left\| \frac{1}{N} \sum_{i=1}^N e^{i\Phi_i(t, f)} \right\|$$

where $\Phi_i(t, f)$ is the time-frequency varying phase of the *i*th response and *N* the total number of trials recorded. The obtained $ITC(t, f)$ ranges from 0 to 1 with 0 for purely non-phase locked activity and 1 for strictly phase-locked activity. Based on ITC, several studies have shown that phase-resetting phenomena are a possible underlying mechanism of sensory brain entrainment (Canavier, 2015). In the case of auditory stimuli, as discussed in the next section, entrainment of oscillations to external rhythms often resulted from the reorganization of the phase spectra rather than a new energy contribution to the ongoing brain activity.

Nevertheless, in practice, demonstrating that brain waves are entrained to specific sensory rhythms is not trivial. It is often unclear whether the observed oscillatory activity in electrophysiological recordings truly reflects the recruitment of endogenous

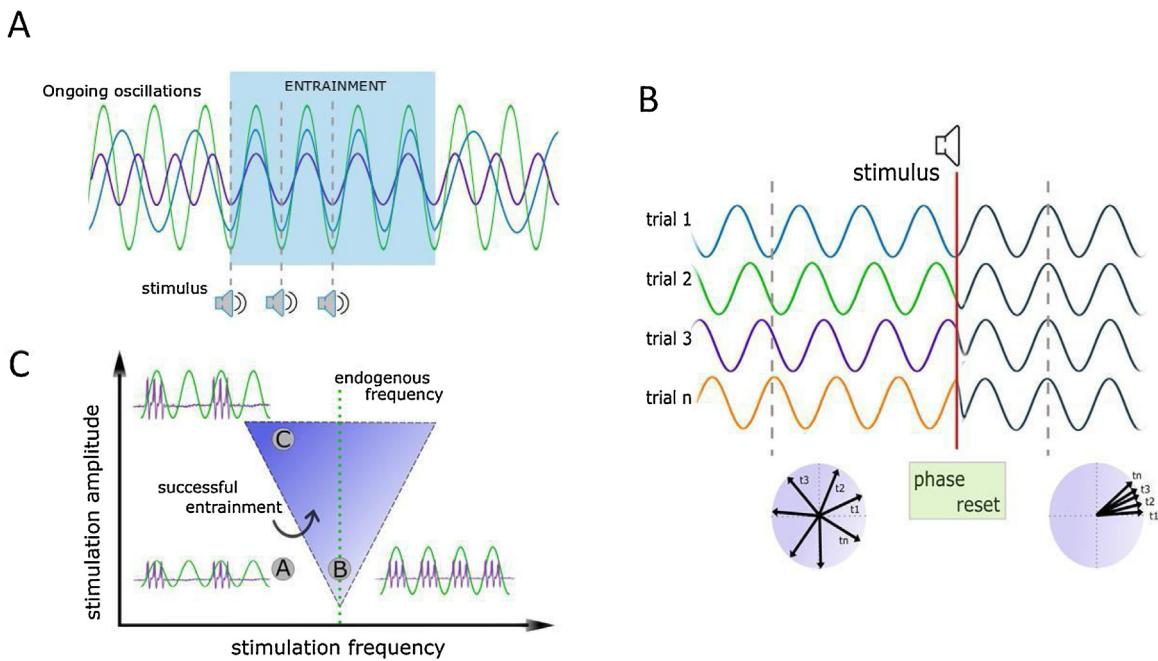


Fig. 2. Phase locking as an entrainment measure.

A. Auditory stimuli presented at a resonant frequency can produce a temporal phase synchronization. This entrainment effect does not necessarily produce changes in signal amplitude at this frequency (green curve). **B.** Entrainment of oscillations to external rhythms can be the result of a phase-resetting phenomenon rather than an amplitude contribution to the ongoing brain activity. The polar diagrams show that the signal phases are synchronized between trials after the sound presentation. **C.** Arnold's tongue, represented by an inverted triangle (in blue), shows the areas where a successful entrainment is possible by changing stimulation amplitude and frequency. Stimulation frequencies other than the frequencies of an endogenous oscillatory activity requires a bigger stimulation amplitude in order to produce an entrainment effect.

neural oscillations by an external periodic drive (Thut et al., 2011). In particular, it is difficult to determine whether SSEPs are not simply reflecting a linear superposition of repetitive transient responses (Hanslmayr et al., 2019). Other arguments supporting entrainment stem from more theoretical considerations about the so-called Arnold tongues (Fig. 2-C). This phenomenon requires plotting the strength of entrainment against stimulation intensity at different frequencies. As observed in a variety of driven systems ranging from fluids to networks of living cells, as the amplitude of the driving force increases, the window of phase-locked activity in response widens around the intrinsic frequency. This prediction would result in a triangular shaped area of entrainment when plotted as a function of driving intensity and frequency called the Arnold tongue (Pikovsky et al., 2003). At the border of this triangular shaped Arnold tongue, entrainment is intermittent by uncoupled time periods, so called phase slips. In other words, the intrinsic oscillator is intermittently coupled to the external stimulation phase for given time periods, until, during constant prevailing stimulation, the internal oscillator slips back to the intrinsic frequency until it is again driven by the external stimulation. Following this idea, experimental work has shown that a visual stimulation at increased intensity causes stronger phase coupling and a greater modulation depth which is in line with the reported concept of the Arnold tongue (Notbohm et al., 2016). This was confirmed by a model network of spiking neurons modulated by various combinations of forcing intensity and frequencies and showing the Arnold tongue in the vicinity of the intrinsic frequency (Herrmann et al., 2016).

4. Entrainment of low-frequency neuronal oscillations to rhythmic sounds

Research using auditory stimuli has focused primarily on entrainment of cortical oscillations to low-frequency rhythmical sounds, particularly when these sounds reflect salient periodicities

like the beat or the meter (Nozaradan et al., 2011; Haegens and Golumbic, 2018). Not surprisingly, the studies reported an increase in EEG signals at specific frequencies corresponding to the perceived beat or meter of the acoustic stimulus (Nozaradan et al., 2012, 2014). When presenting rhythmic stimuli over perceptual detection thresholds, strong ITC was observed at the stimulation rate compared to random stimulus sequences (Will and Berg, 2007). Nevertheless an alignment of endogenous oscillatory activity was also demonstrated for subthreshold stimuli that are not consciously detected (ten Oever et al., 2017). Here low-intensity rhythmic sound patterns induced significant phase locking of low-frequency neural activity (between 1 and 5 Hz), but did not result in any measurable evoked responses, as indexed by broadband ITC and power increase. This suggests that an overt perception of a rhythmic structure is not a prerequisite for neuronal entrainment.

In this context, phase entrainment of low-frequency oscillations to auditory streams has been demonstrated in many previous studies using rhythmic background sounds at delta (1–4 Hz) or theta (2–8 Hz) frequencies, and auditory performance was found to covary with the entrained oscillatory phase (Large and Jones, 1999; VanRullen et al., 2014). Similar findings were found using speech as the entraining stimulus (Ding et al., 2016). Recent data confirmed that delta and theta oscillations are specifically engaged by the quasi-rhythmic properties of speech and can track its dynamics (Giraud and Poeppel, 2012). These findings, together with the fact that the delta and theta bands cover important temporal scales of human speech, suggest that low-frequency phase entrainment may work in amplifying relevant inputs and suppressing irrelevant ones to form predictions and ultimately facilitate and sensory processing (Schroeder and Lakatos, 2009).

Given the fundamental role of low-frequency neuronal oscillations in control of neuronal excitability, entrainment to particular rhythmical sounds has been proposed to underlie selective attention (Calderone et al., 2014). For example, Lakatos et al. (2008) showed for monkeys that neuronal oscillations in primary visual or

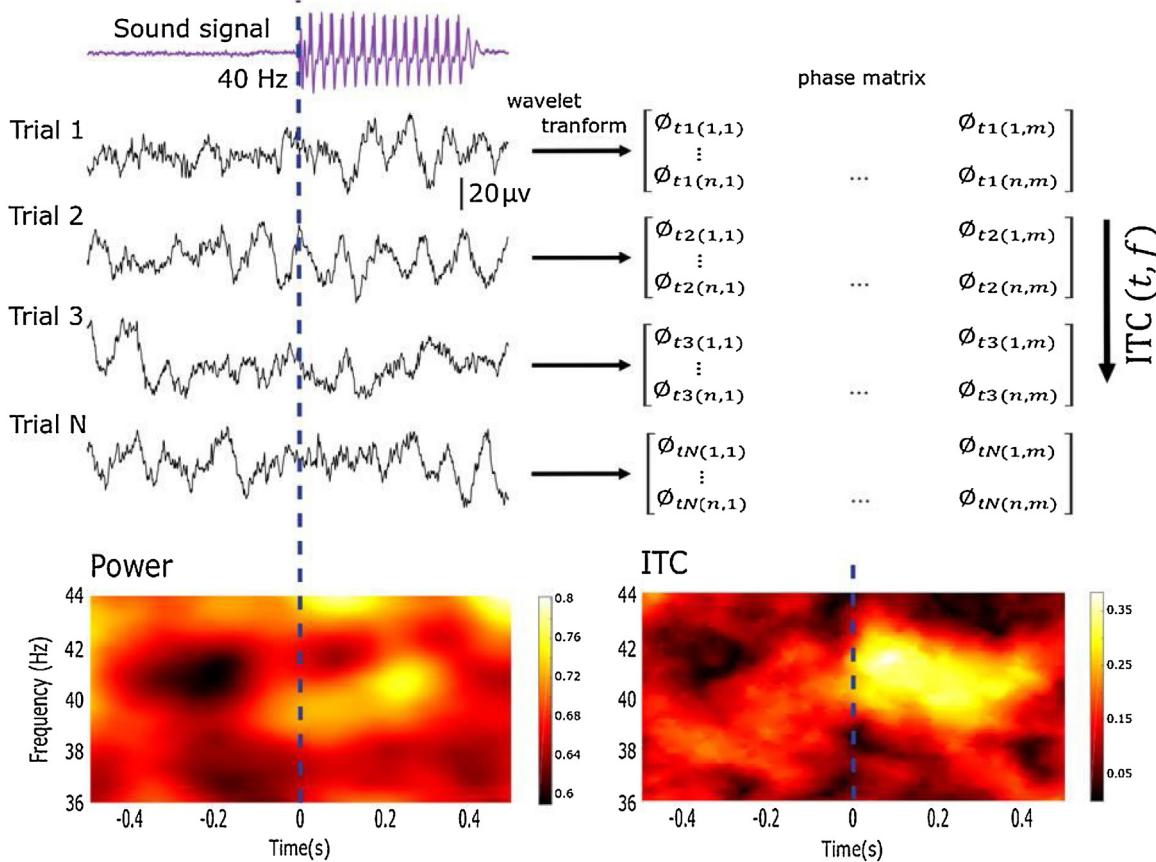


Fig. 3. Power and Inter trial coherence in auditory steady-state response (ASSR).

The wavelet transform allows two characterizations of EEG responses to 40 Hz auditory stimulations. First, a grand-averaged time-frequency maps (left) showing a power increase in evoked energy pooled across 10 participants. Second, an averaging of normalized phase synchronization across trials (right) showing an inter trial coherence. This last measure is significantly higher than evoked energy at stimulus frequency (40 Hz), suggesting a phase alignment of neuronal activity induced by the 40 Hz stimulations.

auditory cortices may entrain to attended rhythmic streams. In particular, when simultaneous but out-of-phase visual and auditory stimulus streams were presented, the phase of ongoing delta oscillations synchronized with the rhythm of the attended stream only, independent of modality. This intermodal selective entrainment effect has been further confirmed in human intracranial recordings (Besle et al., 2011; Gomez-Ramirez et al., 2011). Based on these findings, it was proposed that phase-locking of ongoing low-frequency neuronal oscillations to rhythmic stimuli is a potential mechanism for enhancing perceptual sensitivity (Schroeder and Lakatos, 2009; Calderone et al., 2014).

5. Enhancing gamma oscillations with periodic sounds

Brainwaves have also been shown to synchronize with auditory stimuli with periodicities at 40 Hz frequency (Galambos et al., 1981). The auditory steady-state response (ASSR) can be elicited by a variety of stimuli, including clicks presented at high rates or white noise stimuli amplitude-modulated at high-frequencies (20–80 Hz), where 40 Hz driving appears to produce the largest ASSR in adult studies. Fig. 3 shows the grand-averaged time-frequency maps of stimulus evoked power and ITC of EEG signals during 40 Hz modulated white noise train (Henao et al., 2019). For the ITC wavelet, coefficients with complex numbers were computed and the phase-locking factor was determined by averaging the normalized phase synchronization across trials for every time point and frequency. It can be seen that 40-Hz ASSR is significantly higher in ITC than evoked energy, suggesting a strong phase alignment

of neuronal activity and a weak reflection of the periodicity of the stimulus sequence.

Although the issue is not without controversy, there is gathering consensus that the observed the 40-Hz ASSR arises from both subcortical and cortical generators. Previous studies have localized the generator of the 40-Hz ASSR in a midline brainstem generator with two components (one vertical and lateral) and several cortical sources in medial and lateral sites of Heschl's gyrus (Gutschalk et al., 1999; Herdman et al., 2002). Specifically, in animal models, direct microelectrode recordings into the primary auditory cortex demonstrated an entrainment of local field potential in response to 40-click train stimuli (Nakao and Nakazawa, 2014; Li et al., 2018).

In addition, although the ASSR itself may not reflect cognitive processes, the resonant frequencies of the ASSR suggest that basic neural circuits predominantly oscillate at 40 Hz, and that the ASSR may shed light on the neural circuit functions of auditory-evoked and cognition-related gamma band oscillations. Specifically, gamma oscillations (40–120 Hz), have been implicated in a number of cognitive processes such as sensory binding (Singer and Gray, 1995), attention (Fries et al., 2001), encoding and retrieval of memory traces (Montgomery and Buzsaki, 2007). Furthermore, it has been suggested that networks of GABAergic interneurons and the negative feedback interaction between pyramidal cells and fast-spiking interneurons (e.g. parvalbumin containing cells) are hypothesized to be a key circuitry responsible for gamma band oscillations (Uhlhaas and Singer, 2010). Therefore, this relationship suggests that ASSR activity may serve as a biomarker of the efficiency of inhibitory mechanisms in the brain. Indeed, ASSR are being used increasingly as a marker of brain function and several

studies have found abnormalities in the ASSR in psychiatric disorders like autism (Wilson et al., 2007), schizophrenia (Kwon et al., 1999; Brenner et al., 2009), and bipolar disorder (Maharajh et al., 2007).

Relevant for a functional interpretation, it has been recently reported that 40 Hz acoustic stimulations improve cognition in a transgenic mouse model (5XFAD) of Alzheimer's disease (Iaccarino et al., 2016; Lee et al., 2018; Martorell et al., 2019). Evidences demonstrated that 40 Hz tones entrained gamma oscillations in both the auditory cortex and hippocampal area CA1. Adding a flickering light stimulus at the same time extended the neuroelectric entrainment into brain areas beyond the sensory cortices, inducing gamma oscillations in the medial prefrontal cortex (strongly affected in Alzheimer's disease) and reducing plaques across the whole brain (Martorell et al., 2019). After a week, mice hearing the 40-Hz sounds during one hour per day recognized novel objects and remembered their locations better than mice that received 20- or 80-Hz or random stimulation. Mice with a 40-Hz intervention also found a hidden platform in the Morris water maze faster than unstimulated controls. Finally, plaque number and size fell by about 60 percent relative to controls. Also, microglia appeared enlarged, with shorter, more branched processes, and they consumed more plaques, while astrocytes became up to 20 percent more reactive. A similar effect on microglia and β -amyloid load were also induced by optogenetically driving fast-spiking interneurons at gamma in the hippocampus (Iaccarino et al., 2016), suggesting that sensory entrainment also affects the GABAergic system.

These pre-clinical data suggests that 40 Hz light and sound entrainment may provide a potentially promising non-pharmacological approach to reduce pathogenesis related to Alzheimer's disease. Recently, high intensity 40 Hz light stimulation was investigated in healthy humans and have been shown to induce widespread neuronal entrainment (Jones et al., 2019). Nevertheless, a small pilot study conducted in 10 patients during 10 days using 40 Hz light therapy did not affect amyloid load, as measured by PiB PET (Ismail et al., 2018).

Currently, three clinical trials in the US (called "Overture", "Etude" and "Flicker") combining auditory and visual stimulation are underway and ends in the fall of 2019.

6. Enhancing sleep waves with in-phase rhythmic stimulation

Brain oscillations can be entrained via auditory stimulation not only in the awake brain but also during sleep. Here, during the deepest stages, ongoing cortical activity is characterized by large amplitude EEG slow oscillations (0.5–4 Hz, SOs). These oscillations are generated in neocortical neurons which slowly alternate between phases of membrane depolarization associated with increased firing (up-states) and phases of hyperpolarization with reduced firing (down-states) (Steriade et al., 1993). The up-states give rise to faster oscillations, notably spindles (slow and fast, 9–11 and 11–16 Hz respectively) and high-frequency oscillations (gamma and ripples, 40–120 Hz in humans) (Axmacher et al., 2008; Valderrama et al., 2012; Le Van Quyen et al., 2016) which appear to be of major importance to the role of sleep in cortical function and memory (Rasch and Born, 2013). Therefore, acoustic stimulation in different stages of sleep result in characteristic responses depending the global activity of the brain, but stimulation during deep stages of sleep is the most recognizable because its typical SO shape-like outcome (Weitzman and Kremen, 1965). According with the notion that the brain is more excitable during specific SO phases (Massimini, 2002), several studies found evidence that auditory stimuli arriving during the upward component of the sleep slow waves lead to an enhancement of their ampli-

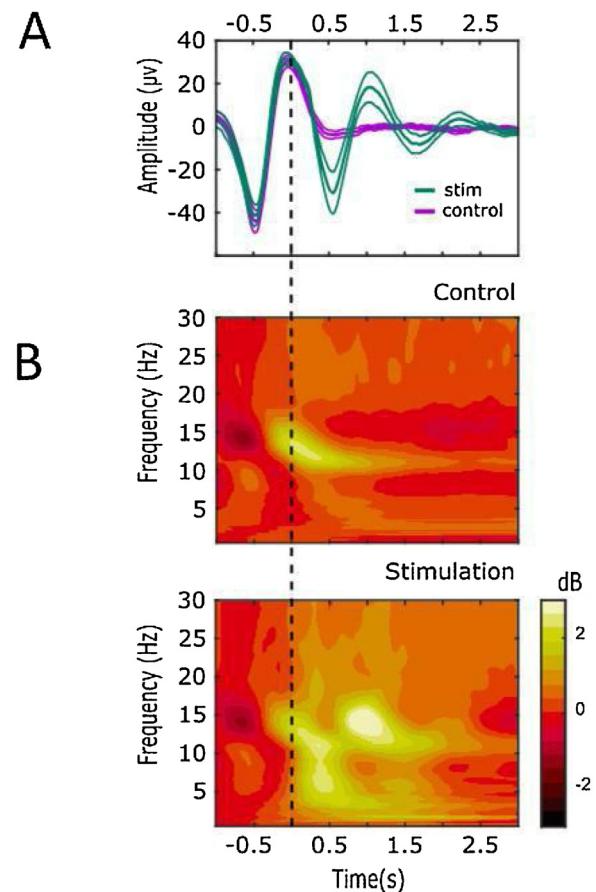


Fig. 4. Slow oscillations enhancement by auditory stimulation. **A.** Delivering an auditory stimulus (black dot line at time 0) during the up-state of the slow sleep oscillation produces an enhancement effect in endogenous activity (green lines, $n = 119 \pm 55.9$ in-phase stimulations and $n = 88 \pm 58.3$ sham stimulations pooled across 10 participants). **B.** TF representations (normalized) show a power comparison between two experimental nights under control and stimulation conditions. For stimulation night, a higher energy is present in several frequency bands (i.e. theta, spindles), suggesting an enhancement not only in slow wave activity but in other endogenous oscillations.

tudes, together with an increase in spindle activity and an improved consolidation of declarative memories (Fig. 4; Ngo et al., 2013, 2015; Ong et al., 2016; Leminen et al., 2017; Papalambros et al., 2017). Presumably, the enhancement of SOs is beneficial because it enhances synchronization between cortical SOs, thalamo-cortical spindles and high-frequency hippocampal ripples during non-rapid eye movement (NREM) sleep (Staresina et al., 2015), although the mechanisms in which the auditory stimulus promotes this oscillatory integration are not clear yet.

Phase-targeted auditory stimulation during slow wave sleep may take advantage of active windows in which the somatosensory cortex is more excitable (Rosanova and Timofeev, 2005). Fig. 4-A shows the averaged signal locked to the stimulus for trials stimulated in the wave peak of the ongoing SOs, and the average response to non-stimulated trials (Navarrete et al., 2019). An increasing of the SO amplitude is noticeable compared to non-stimulation (Ngo et al., 2013). Here, lower frequencies in the SO range respond with both components of typical ERP response, the phase of the ongoing activity is entrained, and the amplitude of the post-stimulus activity is increased (Sauseng et al., 2007). Nevertheless, faster components such as theta and sleep spindles appear as an increased of power on the TF plots as seen in Fig. 4B. As shown, these faster activities are spontaneously locked to SOs, but there is a consequent enhancement of the same activity caused by the stimulus

itself which is not visible in the averaged ERP. This may suggest that sleep activities can be entrained while applying a continuous stimulation which may 'resonate' with the frequency of interest. In fact, experimental evidence has shown that SOs are easily driven by rhythmic auditory stimulation (Garcia-Molina et al., 2018; Simor et al., 2018) although induced spindle responses may follow different dynamics (Ngo et al., 2015). Indeed, it is not possible to entrain sleep spindles by rhythmic clicks in the spindle range (Ngo et al., 2019). This evidence suggests biological limitations to entrain oscillatory activities using rhythmic stimulation in the same frequency range that the target event; particularly, when these activities are originated in deeper structures of the brain (e.g. such as the thalamus). Nevertheless, as the generation of the sleep spindles relies in strong cortico-thalamic dynamics, boosting of sleep spindles may be successful via indirect acoustic stimulation that could activate these thalamocortical paths. For this aim, amplitude modulated ASSR at 40 Hz seems a promising technique (Lustenberger et al., 2018; Henao et al., 2019).

7. Conclusions

Neural oscillations are fundamental to brain function. Today, there is growing evidence demonstrating that rhythmical auditory stimulations can entrain neural network oscillations, providing an efficient way to improve cognitive function or reduce pathogenic processes in the brain. Despite a huge potential, however, standard methods of data analysis are often insufficient for a definite proof of entrainment in some instances. Driven oscillations that vary in frequency over time are not appropriate for traditional analysis like the Fourier transform because such signals violate several underlying assumptions. Therefore, identification and characterization of the temporal dynamics of driven oscillatory responses have motivated, as described in this review, developments of more sophisticated analyses including the time-frequency representation of power or phase. Nevertheless, even with current methods, several interpretative issues remain to be addressed. In particular, one of the most serious problems still to be solved is that to find methods which can unequivocally dissociate between a "real" phase reset and artificial phase concentration due to an additive evoked response. Furthermore, the measures described so far characterize the synchronization of phase and power with respect to a periodic stimulation but always within the same frequency or frequency band. In contrast, another class of measures, broadly referred to as cross-frequency "coupling" of EEG power or phase, are relevant in this context. A driven response representing a coordination of low and high frequencies (such as when high-frequency amplitude depends upon low-frequency phase) may organize brain activity during neuronal entrainment. Of course, in the realm of time-frequency analysis, other new types of relationships can be examined beyond those already mentioned, and novel measures are still being created and explored. Taken together, based on these adapted methods of data analysis, the acquired knowledge paves the way to future clinical applications of sensory entrainment, as numerous psychiatric and neurologic diseases are related to altered brain oscillations.

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