

The Functional Importance of Rhythmic Activity in the Brain Minireview

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Oscillations in brain activity have long been known, but many fundamental aspects of such brain rhythms, particularly their functional importance, have been unclear. As we review here, new insights into these issues are emerging from the application of intervention approaches. In these approaches, the timing of brain oscillations is manipulated by non-invasive brain stimulation, either through sensory input or transcranially, and the behavioural consequence then monitored. Notably, such manipulations have led to rapid, periodic fluctuations in behavioural performance, which co-cycle with underlying brain oscillations. Such findings establish a causal relationship between brain oscillations and behaviour, and are allowing novel tests of longstanding models about the functions of brain oscillations.

Introduction

Ever since Hans Berger first observed rhythmic variations in the human electroencephalogram, around 1929, scientists have been fascinated by the question of whether brain oscillations play a causal role in human behaviour. Over the years, a multitude of studies, supported by significantly improved recording and analysis techniques, have accumulated a wealth of evidence that modulations in the amplitude of specific brain oscillations occur consistently in relation to specific cognitive tasks [1]. Only very rarely, however, has this evidence gone beyond the level of a correlation to establish a clear causal link between brain oscillations and behaviour. Do these oscillations support specific processes, or are they mere epiphenomena? And if the former is true, precisely which computational processes do they implement? How can we make sense out of the myriad of tiny changes in neuronal activity that can be recorded in humans at the neuronal population level through scalp encephalography?

The purpose of this minireview is to highlight recent progress in addressing these fundamental questions with a focus on studies using non-invasive brain stimulation to interact with brain oscillations. Other interesting intervention methods not covered here involve invasive stimulation, such as deep brain stimulation [2] or pharmacological interventions [3]. We begin with a brief introduction to biological oscillations and illustrate how periodic stimulation can reveal the causal or correlative nature of the apparent association between an oscillation and some function, using the circadian rhythm as an example. We then move on to consider longstanding models on the computational role of brain oscillations, detail novel empirical evidence for these models from intervention studies and end with a short discussion of possible mechanisms and therapeutic applications.

Oscillations and Behaviour

Oscillations are ubiquitous in biological systems. In the brain, a large variety of rhythms have been described that differ in their frequency, origin and reactivity to changes in sensory input and task demands [1,4]. Despite these differences, all these rhythms have a number of characteristics in common with each other and with other biological oscillators.

Consider circadian rhythms [5]: like any other rhythm, they are characterised by the periodic re-occurrence of similar patterns at a relatively constant rate (Figure 1). In this case, the expression of biological markers and behaviour, for example being asleep or awake, re-occurs approximately every 24 hours. This periodicity is driven by an intrinsic circadian clock (oscillator), therefore leading to a continuation of the cyclic expression of biological markers (and behaviour) even when the concurrent day–night cycles are perturbed, such as when lighting conditions are kept artificially constant (Figure 1A). After a change of time-zone, however, the circadian clock and associated periodic behaviour eventually align with the new day–night cycle: the oscillator can shift its phase to become synchronised (or entrained) to the new periodic light stimulation, which therefore causes behavioural changes (Figure 1B). This nicely illustrates how periodic stimulation can be used for interventions into the timing of biological rhythms to reveal their causal implication in behaviour.

Similarly, brain oscillations are characterized by rhythmic changes in local field potentials and their frequencies are determined by intrinsic time constants, such as conduction delays, channel dynamics and so on [1]. Do these intrinsic brain rhythms, which cycle in the range of ~0.05–600 times per second [6], also affect behaviour periodically, in a similar manner to circadian rhythms, but at a faster frequency? What functional roles do brain oscillations play, and are they also amenable to controlled interventions through phase alignment by external stimulation?

Orchestrating Brain Processes

One important characteristic of oscillations is their periodicity — the organisation of their temporal dynamics into cycles. Each time point within a cycle is uniquely defined by its phase (ranging from 0–360°, see Figure 1, inset). Oscillations become potentially powerful computational tools when their phase (but also frequency and amplitude) changes due to dynamic modifications in the generating system or in the input [1,7]. In the following, we consider models of possible mechanisms through which oscillatory phase can affect behaviour. All these models rely on a common principle: namely that the oscillatory cycle establishes a recurrent temporal reference frame that allows for the coding of temporal relations between groups of neural elements and between neural elements and the environment. Importantly, this reference frame is not fixed but is subject to dynamic changes (phase resetting).

Oscillatory Phase Representing Cyclic Excitability Changes

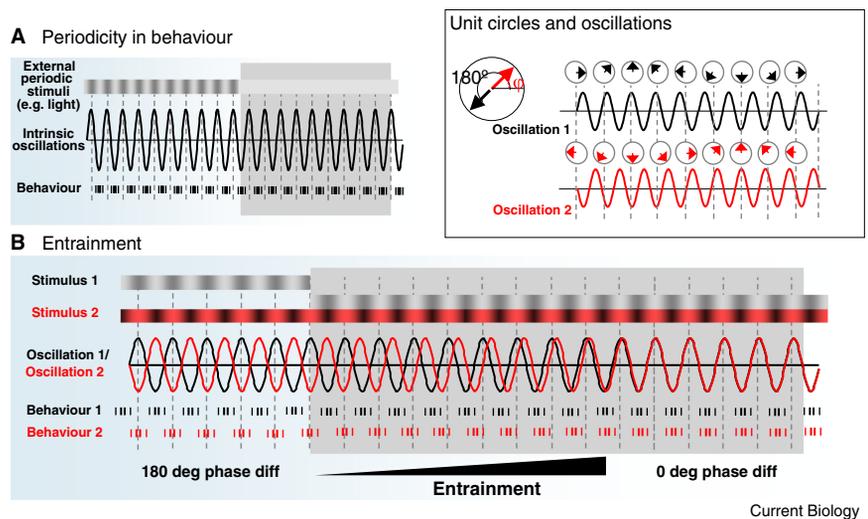
The term brain oscillation typically refers to rhythmic fluctuations in the local field potential (LFP) that can be recorded either directly by an invasive method, or indirectly using

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Figure 1. Oscillations and behaviour.

Inset: Illustration of a simple oscillator model for an introduction of terminology. Biological (and other) oscillators can be described conveniently as vectors rotating counter-clockwise along a unit circle (upper left), whose rates depend on the frequency of the oscillation. Sinusoids (black and red lines) describe the position of the oscillation with respect to phase (φ , 0–360°) within the 360° rotation of one full cycle (y-axis) as a function of time (x-axis). Red and black: two unit oscillators cycling in anti-phase (with 180° phase difference). (A,B) Schematic representation of biological oscillators (here circadian rhythm) and relation to behaviour. (A) Cyclic patterns in behaviour (for example, sleep–wake cycles) are evident even if external light conditions are held constant (grey shade), suggesting the presence of intrinsic oscillators (circadian clocks) which cause periodicity in bodily function.

(B) Cyclic patterns in behaviour (sleep–wake cycles, black colour) realign/synchronize (become entrained) to a new periodic light source (change from black/grey to red light conditions), illustrating that biological rhythms can be entrained by external stimuli.



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magnetoencephalography (MEG) or electroencephalography (EEG). LFPs are caused by synchronous transmembrane currents in populations of neurons and thus represent cyclic changes in the excitability of local neuronal populations. The dependence of excitability on LFP-phase has been characterised by different methods and at different spatial scales. Foremost, invasive recordings have demonstrated that neuronal firing rates are modulated by the phase of LFP oscillations over a wide range of frequencies [8,9].

A second piece of evidence has come from a combined EEG and functional magnetic resonance imaging (fMRI) study [10], in which fMRI responses to a short visual stimulus were measured and the phase of occipital alpha oscillations (~10 Hz) was determined for each stimulus onset from the simultaneously recorded EEG. The results revealed that the amplitude of the visually evoked fMRI response was modulated by the phase of the ongoing alpha oscillations.

Third, cortical excitability can be assessed by means of transcranial magnetic stimulation (TMS). TMS of the occipital cortex induces an illusory flash percept, called a phosphene, the rate of perception of which is a marker of visual cortex excitability. In a simultaneous TMS–EEG study, Dugué *et al.* [11] demonstrated that the rate of phosphene perception depends on the phase of ongoing alpha oscillations.

Finally, recent studies [12,13] have indicated that ongoing oscillatory phase significantly modulates the probability of perceiving a near-threshold visual stimulus. Hence, the phase of ongoing brain oscillations is thought to affect brain processes in a cyclic manner (illustrated in Figure 2A).

Oscillatory Phase Representing (Multiplexed) Phase Coding

The significance of oscillatory phase for information processing goes beyond the cyclic control of excitability. A number of studies [9,14–17] have demonstrated that the timing of spikes with respect to the phase of the oscillations can carry information about sensory stimuli. For example, Kayser *et al.* [14] presented naturalistic auditory stimuli to monkeys and used mutual information to quantify the amount of information about the identity of each stimulus encoded in either phase or amplitude per oscillatory

frequency. Interestingly, the phase of invasively recorded LFP oscillations contained significantly more information than the amplitude, with highest information at low frequencies (4–8 Hz). Another study by the same group [18] related these findings to monkey EEG data and demonstrated that stimuli that could be distinguished from firing patterns could also be distinguished from EEG phase, but not amplitude.

Similar results were reported in a recent human EEG study [19] in which participants were instructed to categorise emotional faces. Correct/incorrect responses were decoded with highest accuracy from the phase of slow oscillations. Interestingly, an information theory analysis revealed that various aspects of the stimulus were encoded in oscillations simultaneously, but at different frequencies. Such multiplexing (schematically represented in Figure 2B) is an efficient coding scheme [15,20], presumably relying on the hierarchical organization of oscillations [8,21].

Oscillatory Phase Representing Communication

Another important computational principle deriving from repeated cyclic changes in excitability has been formalised in the ‘communication-through-coherence’ hypothesis [22]. This hypothesis posits that modulation of oscillatory phase relationships among neuronal populations underlies communication, with communication being facilitated when two oscillatory populations are aligned to their high excitability phases. This theory is based on the fact that brain oscillations represent rhythmic modulations of local excitability, which should affect both the instantaneous probability of spike output from a neuronal population and its sensitivity to inputs [22]. Accordingly, effective communication relies on spikes from the sending population reaching the receiving population at a phase of high excitability. This is the case when both neuronal populations exhibit phase-locked oscillations with a constant phase delay that matches the conduction time from the sending group to the receiving group (exemplified for a phase-delay of zero in Figure 2C). This hypothesis has recently received support from computational models [23,24] and experimental data [25], suggesting that the phase relation between two oscillating neuronal populations modulates communication.

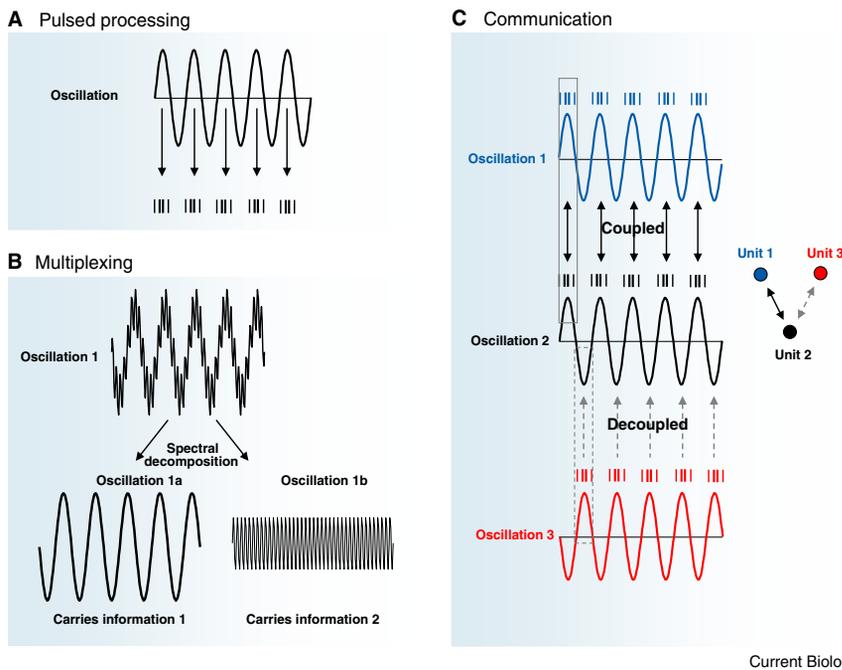


Figure 2. Putative roles of brain oscillations. (A) Pulsed processing. Oscillations in LFP signals represent cyclic changes in excitability that lead to rhythmic changes in firing probability at the frequency of the oscillation. (B) Multiplexing. Brain oscillations are often hierarchically organised with defined temporal relations between high-frequency and low-frequency oscillations. Different information (e.g., different aspects or features of a stimulus) may be coded at the same time but in oscillations of different frequencies. (C) Communication. Dynamic phase alignment between different neural populations may be a mechanism for communication. Here, oscillation 1 is phase-locked to oscillation 2 such that spikes from one oscillatory element arrive at the other element at phases of high excitability. In contrast, spikes arriving at times of low excitability have less impact on the receiving element (oscillation 2 versus 3).

Interventions: Cyclic Behavioural Changes at Brain Oscillation Frequencies

If brain oscillations causally modulate behaviour (and if external stimuli

Similarly, several MEG/EEG studies have demonstrated that changes in synchronisation between distant brain areas (possibly reflecting communication) are systematically related to task performance [26,27], constituting a possible mechanism for implementing the gating of information flow, feature binding or cross-modal integration among neuronal populations [7,28,29].

In summary, oscillations can contribute to information processing in the human brain in various ways by creating a flexible temporal reference frame (at multiple temporal scales) and by temporally aligning phases of high excitability between neural populations (or to sensory input). But can we externally modulate the phase of oscillations causing behavioural changes?

Inferring Functions from Effects of Interventions

We shall now consider recent studies in which external, non-invasive brain stimulation was used to interact with ongoing brain oscillations. Such interventions can involve sensory inputs reaching the brain via sensory pathways (Figure 3A), or the application of non-invasive brain stimulation techniques such as TMS (see Figure 3B) or transcranial alternating current stimulation (tACS, see Figure 3C) that directly stimulate the cortex and therefore bypass sensory pathways. Can external stimulation interact with brain oscillations in the way that changes in light exposure affect the circadian rhythm, but on a different time scale? This seems indeed to be the case. In line with longstanding models of the generation of evoked brain responses by external events (for detailed accounts see [30,31]), recent research has shown that external sensory and TMS stimuli involve the reorganization of ongoing oscillations through phase-locking [32–34], whereas tACS reinforces the membrane potential to oscillate promoting neural activity to resonate at the given stimulation frequency [35]. These findings demonstrate how established (TMS or tACS) techniques [36,37] can be used in novel ways for the study and controlled manipulation of human brain oscillations.

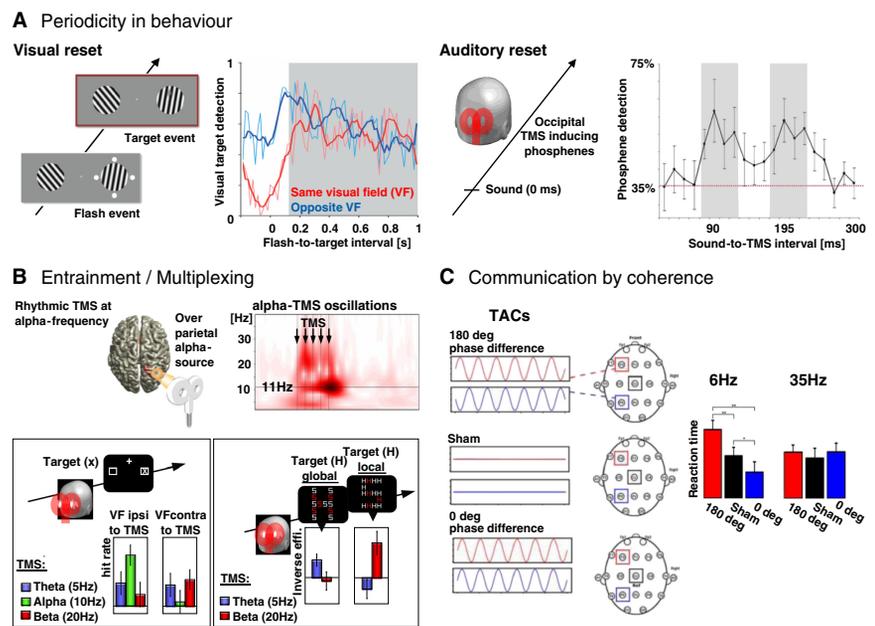
phase-lock ongoing oscillations to stimulus onset), then these oscillations may become visible in time-resolved measures of behavioural performance. It should suffice to sample task performance after each phase-reset at a sufficiently high temporal resolution across trials, to reveal the cyclic nature of the associated processes (by reconstructing a performance curve over time from each sample across all trials).

In one recent study, Landau and Fries [38] tested visual performance at two opposite stimulus positions, after resetting attention to one of them by presenting brief flash cues at one location (Figure 3A). Visual performance was then examined over a one second time window locked to this reset event (with data points being acquired in steps of 16.7 ms). This revealed a cyclic pattern in detection performance (after an initial visual masking effect), waxing and waning with a frequency of 4 Hz per stimulus position (Figure 3A), in anti-phase between the two, opposite stimulus locations (Figure 3A, compare red versus blue line). With two sampled positions, this indicates that the brain samples information at 8 Hz (2 x 4 Hz). These data are consistent with previous findings about the periodicity and rate of attentional processes [39]. Although the authors did not record EEG [38], it is worth noting that ongoing phase variability of brain oscillations in the theta- (4–8 Hz) and alpha- (8–14 Hz) bands have been related to visual perception and attention variability (for example, [12,13]). This points to a possible link between the observed periodicity of perception and brain oscillations.

Inspired by pioneering animal work on cross-modal phase-alignment of ongoing oscillations in sensory areas [32], another recent study [33] used sounds to phase-lock visual performance in time, while simultaneously recording EEG. Romei *et al.* [33] presented a brief (14 ms) sound and measured fluctuations in subsequent visual perception from phosphenes evoked by TMS over visual cortex. The data-points were acquired in steps of 15 ms and revealed a cyclic pattern in phosphene perception at ~10 Hz locked

Figure 3. Modifying brain oscillations by external brain stimulation to reveal their causal roles.

(A) Sensory stimulation. Phase-locking of attention to a spatial position by a flash event or to a time-point by a sound reveals cyclic patterns in visual task performance at frequencies of brain oscillations. (B) Rhythmic transcranial magnetic stimulation (TMS). Upper panel: rhythmic TMS tuned to the parietal alpha-frequency can entrain parietal alpha-generators. Lower panels: rhythmic TMS over parietal cortex at specific frequencies can bias perception towards specific (left-right) spatial locations (interventions into brain oscillations of location-based attention, left) or towards specific (local-global) stimulus features (interventions into brain oscillations of feature-based attention, right). Y-axis: Values above the zero line correspond to better behavioural performance (left plot: hit rate normalized to sham TMS, positive values upward, right plot: inverse efficiency (reaction time/hit rate) normalized to sham TMS, negative values upward). (C) Transcranial alternating current stimulation (tACS) over two areas (frontal-parietal) improves working memory performance when the protocol is designed to synchronise these areas at theta-frequency (0° phase difference) but impairs performance when it desynchronises these areas at theta-frequency (180° phase difference). Y-axis: Higher values correspond to longer reaction times and thereby poorer behavioural performance. (A), left, adapted from [38]; (A), right, adapted with permission from [33]; (B), upper panel, adapted from [34]; (B), lower panels, adapted from [41,43]; (C), adapted from [44].



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to sound onset — a perceptual rhythm in the alpha-band (Figure 3A, right).

The common observation across these two studies [33,38] is therefore that interventions by sensory stimulation revealed perceptual fluctuations cycling at rapid frequencies, similar to those of brain oscillations. In addition, Romei *et al.* [33] simultaneously recorded brain waves with EEG and demonstrated that the phase dynamics and frequency of perception matched those of underlying occipital alpha oscillations. These findings hence link the behavioural (perceptual) 10 Hz rhythms more firmly to intrinsic, ongoing brain oscillations.

Interventions: Multiplexing in the Attention Network

Recent studies using rhythmic TMS have suggested that stimulation of the parietal cortex with a periodic electromagnetic force can be used to entrain brain oscillations [34]. Stimulation at the frequency of the underlying brain rhythms (at the alpha-frequency) leads to a progressively enhanced oscillatory response at this frequency (Figure 3B, upper panels), and this effect resulted from direct TMS interaction with the underlying neuronal population (for details see [34]).

If the oscillatory response to rhythmic TMS reflects entrainment (or synchronisation) of a natural brain rhythm, rhythmic TMS should then lead to meaningful behavioural changes, provided there is a causal relationship between brain oscillations and function. This was tested for parietal cortex rhythms previously linked by EEG/MEG evidence to attention. One of these rhythms is the posterior alpha-oscillation, the lateralization over parietal cortex of which has previously been identified as an EEG/MEG-fingerprint of visual spatial attention, predicting forthcoming perception at specific spatial locations [40]. In line with these EEG/MEG results, rhythmic parietal TMS at alpha-frequency over one hemisphere differentially affected target detection

in the contra- versus ipsi-lateral visual fields [41]. Alpha-TMS biased perception away from the contra- towards the ipsi-lateral visual field (relative to rhythmic TMS at control flanker frequencies; Figure 3B left), causally implicating parietal alpha-oscillations in the control of visual perception across space. In contrast, parietal beta- and theta-oscillations have been identified as an EEG/MEG-fingerprint of perceiving local versus global image features [19,42]. Accordingly, rhythmic TMS at beta versus theta frequencies over the right parietal cortex benefited local versus global perception [43], consistent with a causal relationship between theta/beta-oscillations and the encoding of global/local image information respectively.

These results further support the notion that non-invasive brain stimulation can be used to entrain (synchronise) brain oscillations, creating natural oscillatory fingerprints and causing specific behavioural changes. Entraining distinct oscillations of an attentional node (parietal cortex) by specific TMS intervention biased perception of the participants towards specific visual locations or features. This finding hence suggests that different aspects of a stimulus are encoded in distinct parietal oscillations, in line with multiplexing of information and possibly reflecting hierarchically organised networks resonating at different frequencies.

Interventions: Phase Coupling/Decoupling between Two Nodes of a Network

The above results suggest that rhythmic external stimulation can be used to synchronise brain oscillations in one brain area in a functionally meaningful way. The next question then is whether the simultaneous, rhythmic stimulation of two areas in an in-phase or out-of-phase regime would lead to behavioural effects that support functional coupling or decoupling of these areas by their respective phase-relationship. To address this question, Polanía *et al.* [44]

stimulated the fronto-parietal network using tACS through one frontal and one parietal electrode (Figure 3C). The rationale was to synchronise/desynchronise these two areas at theta-frequency (6 Hz) and to assess the consequences on working memory, based on the common EEG/MEG-finding of enhanced fronto-parietal theta synchronisation (coherence) in tasks engaging working memory (and other central executive functions).

Polanía *et al.* [44] found that synchronising these two areas at 6 Hz improved reaction time in a working memory task relative to sham stimulation (Figure 3C, 6 Hz, blue bar, 0° phase difference) but desynchronisation at this frequency deteriorates performance (Figure 3C, 6 Hz, red bar, 180° phase difference), whereas no change was observed upon stimulation at a control frequency (Figure 3C, 35 Hz). These results support the communication-through-coherence model and indicate that rhythmic external stimulation may be used to induce inter-areal synchronisation or desynchronisation at behaviourally relevant frequencies.

We note that across the interventional studies reviewed here, phase-locking between oscillations and perception/working memory is mainly confined to lower frequencies below the gamma range (<30 Hz). This can be due to an experimental bias, such as phase-locking in gamma being more difficult to investigate by interventions, or gamma frequencies being devoted to other tasks not yet investigated by interventions. Two recent studies [45,46] seem to speak against gamma-frequencies not being amenable to interventions, reporting gamma-specific tACS-effects on perception or motor performance.

Short versus Long Lasting Effects of Interventions

What are the possible mechanisms by which brain stimulation might interact with ongoing brain oscillations? We here briefly consider two such mechanisms. First, when few stimuli or short blocks of stimulations are used (as in most of the interventional studies mentioned above), the main mechanism of action may be acute in nature, and consist of the instantaneous and transient interactions with ongoing brain oscillations through the synchronisation (or desynchronisation) of firing activities within one or several neuronal populations generating these oscillations. This may facilitate (or hinder) ongoing routing of (specific) information across the network in the short-term — concurrent to stimulation, and serve to test models of brain oscillations.

Second, longer and recurring blocks of rhythmic brain stimulation will likely induce more long-term neuroplastic changes [35,36,44] in line with long-term potentiation and depression and spike-time dependent plasticity at the synaptic level [47].

Therapeutic Implications

Might these new interventional approaches into brain oscillations have therapeutic implications? There is evidence that certain brain disorders are associated with abnormal neural synchronisation [48]. Therefore, precisely timed interventions to appropriately synchronise (but also desynchronise) these oscillations may well result in neural changes promoting recovery. Acute effects may serve to establish a causal relationship between pathological oscillations and brain dysfunction, and thereby highlight specific brain rhythms as possible therapeutic targets, while longer-term induced changes may support recovery *per se*.

One example is exaggerated beta-oscillations in the motor system of Parkinson's disease patients, which have been related to akinesia (for example, [49]). Because driving motor cortex with rhythmic tACS at gamma-frequency can enhance motor performance in healthy adults [45], in contrast to beta-stimulation, which slows voluntary movements [45,50], it has been proposed that targeted manipulations of these rhythms may help patients with motor deficits [45]. Other applications are conceivable, given the evidence of abnormal synchronisation of brain oscillations in other brain disorders [48]. Further studies into brain oscillations as a possible target of therapeutic interventions are clearly needed.

Conclusion

Our understanding of human brain rhythms and functions has advanced considerably in recent years. Controlled modulation of brain oscillations holds promise to further this knowledge. Recent findings have demonstrated that phase-aligning these oscillations through brain stimulation can reveal their periodicity, characterised by recurrent peaks and troughs, even in behavioural measures. This is consistent with the idea that oscillatory phase causally shapes brain function. Other studies have revealed that synchronising brain oscillations in specific frequency-bands within or across brain areas leads to changes in perception, attention and working memory that are in accord with brain oscillations supporting multiplexing of information and inter-area communication. Therefore, brain oscillations seem to be fundamental for perception, cognition and behaviour (as opposed to be merely epiphenomenal), and appear amenable to controlled intervention for a modulation of brain function and dysfunction.

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