INTRODUCTION

In order to accomplish tasks at fast time scales, the brain not only relies on biochemical mechanisms but also electrical ones. Therefore, electrophysiology is a critical component in efforts to understand how the human brain works. Brain rhythms, or neural oscillations, are the prominent features of macroscale electrophysiological recordings, and they are thought to be implicated in virtually every behavior and neuropathology (Buzsáki and Draguhn, 2004). While structural changes to the brain happen on relatively long time scales, oscillations are theorized to support mental functions that require dynamically switching between functional neural circuits (Fries, 2005; Womelsdorf et al., 2014; Voytek and Knight, 2015). While evidence for causal or mechanistic roles of neural oscillations is currently limited, correlational studies have shown promise for the importance of various brain rhythms. I became interested in how oscillations relate to mental processes such as memory (Klimesch, 1999) and disorders including Parkinson’s disease (de Hemptinne et al., 2013). Recording brain rhythms has proven useful toward developing biomarkers of neurological diseases (Buzsáki and Watson, 2012) and for training successful brain-machine interfaces (Leuthardt et al., 2004).

Rhythms in neural activity are observed across various temporal and spatial scales (Buzsáki and Draguhn, 2004). Traditionally, neural oscillations have been clustered into canonical frequency bands, including delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (15-30 Hz), gamma (30-90 Hz), and high gamma (>50 Hz). These bands roughly correspond to frequency ranges commonly observed in human electroencephalography (EEG). Though they have been observed for nearly a century, recent theories suggest that these oscillations play an active role in neural communication (Fries, 2005).

One prominent theory is that oscillations accomplish this function using cross-frequency coupling, in which multiple neural oscillators in different frequency ranges interact with one another (Canolty and Knight, 2010). To characterize this coupling, the phase and amplitude properties of each oscillator are calculated using spectral analysis. A key feature in all spectral analysis methods is that they inherently assume that the fluctuations in brain activity over time can be characterized using a sinusoidal basis. That is, the underlying assumption is that the complexities of oscillatory brain activity are best captured by sinusoidal oscillators. A sinusoid (or sine wave) is a smoothly-varying rhythmic signal governed by a mathematical equation. However, the focus of this thesis is that neural oscillations are commonly nonsinusoidal. Rather than being a nuisance, I argue that these nonsinusoidal features may contain critical physiological information about the neural systems and dynamics that generate them. My goal is to address the inconsistency between standard neural analysis approaches and the observed nonsinusoidal shapes of oscillatory waveforms, which is particularly highlighted in Chapter 1.

I begin by reviewing a diverse set of examples of nonsinusoidal oscillations across species and brain regions in this introduction. Interestingly, studies published prior to the modern proliferation of advanced computation focused more on raw, unfiltered data, by necessity. In contrast, recent studies tend to focus on heavily processed data and lack attention to the oscillatory waveform shapes. I discuss past methodological approaches for characterizing nonsinusoidal features of neural oscillations, as well as adaptations to traditional spectral analysis to account for nonsinusoidal waveforms. In Chapter 2, I outline and motivate our proposed cycle-by-cycle approach for analyzing the waveform shape of brain rhythms. In Chapter 3, I apply this method to explore if waveform shape contains information about local neuronal firing patterns. Combining waveform shape analysis with a modern understanding of the physiological generators of neural oscillations can provide an entirely new framework for understanding the physiological basis of neural computation and cognition.

**Nonsinusoidal waveforms are stereotyped**

One strong indication that the waveform shape of neural oscillations contains physiological information is that features of these waveforms are stereotyped across recordings. This consistency indicates that the waveform shape reflects something specific about the physiology of the recorded brain region. Here I review several examples of this phenomena.

In human electrophysiology, oscillations with stereotyped nonsinusoidal shapes include the sensorimotor “mu rhythm,” motor cortical beta oscillation, and cortical “slow oscillations”. The mu rhythm oscillates at an alpha frequency (around 10 Hz) and was named because its waveform shape resembles the Greek character μ (Fig. 0.1A). It is characterized by the fact that one extremum (e.g., its peak) is consistently sharper than the other (e.g., its trough); it is also described as an arch, comb, or wicket shape (Kuhlman, 1978; Tiihonen et al., 1989; Arroyo et al., 1993; Salmelin and Hari, 1994; Pfurtscheller et al., 1997, 2006; Muthukumaraswamy et al., 2004).

In addition to the sensorimotor mu rhythm, we have recently highlighted that motor cortical beta oscillations also have striking nonsinusoidal features (see Chapter 1). These beta oscillations manifest a sawtooth shape, in that their voltage either rapidly rises before more slowly falling off, or vice versa (Fig. 0.1B).

In contrast to these faster rhythms, “slow oscillations” are low-frequency rhythms (<1 Hz) that dominate across the cerebral cortex during anesthesia and natural sleep (Steriade et al., 1993; Amzica and Steriade, 1998, 2000). Slow oscillations are distinguished by alternating periods of depolarization (up states, positive half-wave in surface EEG) and hyperpolarization (down states, negative half-wave in surface EEG) (Amzica and Steriade, 1998). The negative half-waves are consistently sharper than the positive half-waves, again resulting in a stereotyped arch-like shape (Mölle et al., 2002; Massimini et al., 2004; Clemens et al., 2007; Ngo et al., 2013). Because the waveform shapes of these oscillations are relatively conserved across brain regions, people, and even species, we reason that these oscillation features likely contain information about the oscillatory generators. Due to the assumptions of standard sinusoid-based spectral analyses, these potentially critical nonsinusoidal features will be lost or overlooked.

Animal models also give us an opportunity to invasively record nonsinusoidal oscillations often not feasible to record in humans. Hippocampal theta oscillations, for example, are among the most studied rhythms in the local field potential (LFP); they have a stereotyped sawtooth shape (Fig. 0.1C) (Green and Petsche, 1961; Artemenko, 1973; Buzsáki et al., 1985; Belluscio et al., 2012; Dvorak and Fenton, 2014; Lockmann et al., 2016). Similarly, respiratory rhythms in the olfactory bulb are also sawtooth-like in shape (Buonviso et al., 2003; Lockmann et al., 2016). While slow oscillations are arch-shaped when recorded with macroelectrodes, those recorded in the LFP have complex and diverse shapes, with sharp transitions between the up and down states (Fig. 0.1D) (Amzica and Steriade, 1998; Fröhlich and McCormick, 2010; Lockmann et al., 2016; Ouedraogo et al., 2016). These invasive recordings present a unique opportunity to extract information from waveform shape because of their closer proximity to the signal source.

If an oscillation’s waveform shape reflects physiology that is truly evolutionarily conserved, we expect to see similar waveform features in analogous oscillations across species. One example of such conservation is the stereotyped sawtooth waveform of the hippocampal theta rhythm is observed in rabbit, mouse, and rat (Bland et al., 1980; Buzsáki et al., 1985, 2003). Also, the arch-shaped alpha-frequency oscillations observed in rat somatosensory cortex, which have been hypothesized to be analogous to the previously mentioned mu rhythms in EEG (Wiest and Nicolelis, 2003; Fransen et al., 2016). Additionally, slow oscillations are also arch-shaped in surface EEG in the anesthetized cat (Amzica and Steriade, 1998), to give but three examples. Concerning slow oscillations, Amzica & Steriade presaged in 1998 that “Fourier spectra are not able to discriminate between periodic phenomena and waves with a given shape,” noting that analyses “should take into consideration the actual aspect of waves and, if possible, their relationship with the state of the cellular aggregates of the corticothalamic network” (Amzica and Steriade, 1998). Here I extend this sentiment to all neural oscillations.

In addition to the variety of empirical reports, theoretical estimates of field activity acquired through computational modeling are also notably nonsinusoidal. A common method for simulating gamma oscillations, for example, is the biophysically-inspired pyramidal-interneuron gamma (PING) cortical model. In a morphologically-realistic simulation of the LFP, gamma oscillations show a sawtooth-like waveform shape; while the decay phase was very short, the voltage rise had an exponentially decaying trajectory, analogous to synaptic currents (see Fig. 0.1E). In comparison, a slightly different implementation of the PING model yielded gamma oscillations with an arch shape (Lowet et al., 2016). The different oscillatory shapes generated by different PING models are driven by differences in the defined biophysical parameters, hinting at a link between biophysics and waveform shape.

Other computational models of neural oscillations are more abstract and do not directly simulate the synaptic currents that largely underlie the LFP. Still, the waveform generated by a Morris-Lecar model (Somers and Kopell, 1993) (Fig. 0.1F, top) has a strikingly similar waveform to the slow oscillations shown in Fig. 0.1D. By changing the parameters of the model oscillators, researchers can fit simulated waveforms to those recorded in the LFP. In theory, this technique of altering biophysical parameters in LFP simulations to fit waveform shape can be inverted to try and infer biophysical parameters from the LFP. This could prove to be an enticing extension to the common analytic toolkit used to study oscillations, moving beyond standard spectral analyses to more physiologically informed approaches.



**Figure 0.1.** Oscillatory waveforms are nonsinusoidal in many neural recordings and simulations. (a) The mu rhythm, a motor cortical oscillation with power at 10 Hz, is characterized by its sharp extrema which produce an arch shape. (b) Beta oscillations in the human primary motor cortex (ECoG) have sharp and sawtooth-like features. Produced by the authors. (c) Theta oscillations in the rodent hippocampus have a sawtooth-like waveform in which oscillatory rises are steeper than decays. (d) Slow oscillations is the neocortex have complex waveforms that contain aspects of arches, sawtooths, and rectangular waves. (e) Gamma oscillations produced by the pyramidal-interneuron gamma (PING) mechanism. Field potentials were generated both in a population of morphologically realistic neurons (black) and by using a weighted sum of synaptic currents (red). In both cases, the waveforms had an asymmetric shape: a sharp voltage drop followed by an exponential-shaped voltage rise. (f) The waveform shape of a conductance-based Morris-Lecar oscillator model changes with the lambda parameter (top: ƛ=0.02, bottom: ƛ=0.33), though they are never truly sinusoidal. Note that the top example is strikingly similar to the temporal dynamics of slow oscillations recorded in the parietal cortex of rats (see panel d). (g) An example of the occipital alpha that appears to have a shape that is more triangular than sinusoidal.

**Methods for characterizing nonsinusoidal oscillations**

Given the numerous examples of stereotyped oscillatory waveforms described above, metrics have been developed to quantify the features of the waveform shape, though they are underutilized. We recently quantified the sharpness of peaks and troughs by calculating the short-term voltage change around each extrema in the raw trace (see Chapter 1). The ratio between peak and trough sharpness was shown to differentiate neural activity between neurological treatment conditions in Parkinson’s disease. In addition to the symmetry of oscillatory peaks and troughs, other studies have quantified the symmetry between the rise and decay phases to determine how rapidly the voltage rises compared to its decay time. The ratio between the rise time and decay time has been used to quantify the sawtooth nature of the hippocampal theta rhythm, where the rise phase is consistently shorter than the decay phase (Belluscio et al., 2012; Dvorak and Fenton, 2014). Similarly, a “slope ratio” has been used to compare the steepness of the rise period to that of the adjacent decay period (Lee and Jones, 2013). While promising, these metrics do not capture the full space of possible waveform features, so more approaches will need to be developed to further characterize oscillatory waveforms. Links between nonsinusoidal waveform shape and physiology will be more accurate by measuring multiple waveform features.

In addition to quantifying features of the waveform shape, methods have been developed to account for nonsinusoidal waveforms when performing traditional spectral analysis. Nonsinusoidal oscillations have been shown to generate unintuitive phase and amplitude estimates (Dvorak and Fenton, 2014; van Driel et al., 2015; Amiri et al., 2016b; Jones, 2016). The amplitude of high frequency oscillations is spuriously increased when filtering sharp transients (Amiri et al., 2016b). To correct for this, a classifier was developed to differentiate sharp events with and without high frequency oscillations (Amiri et al., 2016b). Because the hippocampal theta waveform has such a striking sawtooth shape, some researchers studying the phase of this oscillation have developed alternative waveform-based phase estimates that interpolate between empirically identified time points, including extrema and zero-crossings (Siapas et al., 2005; Belluscio et al., 2012; Dvorak and Fenton, 2014; Trimper et al., 2014). Using this approach, it was shown that decoding of a rat’s spatial position is improved by referencing spiking to this alternate phase estimate as compared to traditional sinusoidal phase estimates (Belluscio et al., 2012).

Because both phase and amplitude estimates can be unintuitive for nonsinusoidal oscillations, waveform shape is an important consideration in phase-amplitude coupling (PAC) analysis, which quantifies the correlation between the phase of one oscillator and the amplitude of a higher-frequency oscillator. Past studies have provided various recommendations for assessing whether PAC is true or spurious (Kramer et al., 2008; Ray and Maunsell, 2011; Aru et al., 2015; Gerber et al., 2016; Jones, 2016; Lozano-Soldevilla et al., 2016; Vaz et al., 2017). Here I suggest that the spurious/non-spurious dichotomy may not be useful, as “spurious” implies uninformative. In contrast, I argue that apparent PAC that arises from nonsinusoidal features is still a valid measure of signal properties, though the biophysical interpretation may differ depending on the waveform properties that give rise to the observed PAC. That is, statistically significant PAC may not indicate two interacting oscillators at different frequencies, but rather may reflect one regular nonsinusoidal oscillator.

PAC methods have been recently adapted to account for nonsinusoidal oscillations. Because nonsinusoidal oscillations produce a nonuniform distribution of instantaneous phase, PAC estimates may be biased, and a correcting factor based on phase nonuniformity was suggested (van Driel et al., 2015). This nonuniform phase distribution also confounds analyses of phase-locked spiking, which can be appropriately addressed using surrogate statistics (Sigurdsson et al., 2010). As for amplitude estimates, the previously mentioned classifier that detects true high frequency oscillations was applied to assess PAC changes while avoiding the confounding effects of sharp transients (Amiri et al., 2016a). Ultimately, measuring the waveform shape of oscillations would clarify the implications of PAC estimates.

While nonsinusoidal oscillations are not parsimoniously captured in the components of the Fourier transform, alternative decomposition methods have been applied to study neural oscillations (Mäkinen et al., 2005; Chandran K S et al., 2016). In contrast to techniques like the Fourier transform, the matching pursuit algorithm decomposes the signal using transient broadband functions in addition to narrowband functions, making it suitable for capturing physiologically-informative sharp waveform features (Chandran K S et al., 2016). Another approach, empirical mode decomposition (EMD), decomposes a signal into rhythmic components based on local extrema rather than sinusoidal components. One study showed that EMD improved the frequency resolution of coupling in both simulated data and mouse hippocampal recordings (Pittman-Polletta et al., 2014). EMD was also applied to analyze amplitude-amplitude coupling in an attempt to account for the fact that such coupling is positively biased by nonsinusoidal and nonstationary oscillations (Yeh et al., 2016). Thus, decomposition methods that do not assume a sinusoidal basis may be more appropriate for analyzing the spectral properties of oscillations with a nonsinusoidal waveform shape.

While such approaches require multiple oscillatory cycles to yield useful metrics, studying the temporal dynamics of single oscillatory cycles can also reveal critical physiological information, as previously suggested (Artemenko, 1973; Jones, 2016). The fast (30-60 Hz) arch-shaped oscillations produced in response to cortical injury in the rabbit are relevant here (Adrian and Matthews, 1934). At the start of injury, monophasic spikes appear in isolation but gradually become broader and more frequent, generating an arch-shaped oscillation, followed by a quasi-sinusoidal oscillation. From a nonsinusoidal perspective, each period of the oscillation has its own interesting temporal dynamics. Therefore, analysis of each period as an individual event may be more appropriate than analyzing the series of events as one oscillatory process.

**Distinguishing different oscillatory processes by waveform shape**

The aforementioned methods for quantifying the features of oscillatory waveforms can be used to distinguish between oscillatory phenomena that appear at similar spatial locations at the same frequency but have different physiological origins. Because distinct neural processes can co-exist in the same frequency band, applying a narrow bandpass filter may make multiple distinct oscillatory processes indistinguishable from one another. For example, in the rat gustatory cortex there are three alpha frequency rhythms that appear to be distinct because they occur at a specific time during a sensory experience and can be distinguished by their waveform shape in addition to their center frequency and amplitude (Tort et al., 2010).

Similarly, two of the earliest identified signals in human EEG were the visual cortical alpha oscillation and the aforementioned sensorimotor mu rhythm. Because of their sometimes overlapping spatial topographies and frequencies (8-12 Hz), the two oscillations can be misidentified and confused with one another (Pineda, 2005). However, an important difference between these two rhythms is their waveform shape. As mentioned above, the mu rhythm has an arch-like waveform while, in contrast, the occipital alpha oscillation has a more symmetric waveform that even appears characteristically triangular in some raw traces (Stam et al., 1999) (Fig. 0.1G). These differences in shape likely reflect differences in the properties of these two oscillatory generators. The sharp transient of the mu rhythm is hypothesized to reflect a current source in the primary somatosensory hand area (Tiihonen et al., 1989). The occipital alpha oscillation may manifest as a smoother waveform because the underlying current source is less temporally synchronous. This hypothesized difference in physiology is analogous to previous hypotheses regarding the differences in the shapes of slow oscillations (Amzica and Steriade, 1998).

In addition to slow oscillations, 1-5 Hz sawtooth-shaped waves also occur in human EEG and are particularly associated with REM sleep (Berger et al., 1962; Pearl et al., 2002; Louis et al., 2004). Noting the shape of this rhythm has helped associate it with distinct behaviors and mechanisms that would not have been possible if it was simply filtered and identified as a “delta oscillation.” Additionally, sleep spindles are characterized as bursts of 8-14 Hz oscillations that are observed during sleep, along with slow oscillations and sawtooth waves. Sleep spindle subtypes can be distinguished by their shape (Pavlov et al., 2012).

**Oscillation waveform shape relates to physiology**

Robust differences in the waveform shapes of the oscillations mentioned above can be assumed to represent differences in properties of their underlying generators. For example, the sharp transients that occur in spike-wave discharges, as well as in an alpha rhythm in the gustatory cortex, correspond to synchronous local spiking (Coenen and Van Luijtelaar, 2003; Slaght et al., 2004; Fontanini and Katz, 2005; Fabricius et al., 2008). In contrast, the smooth “wave” component of the spike-wave discharge coincided with a slow depolarization of layer 5/6 neurons (Polack et al., 2007). The “spike” portion of this waveform was preceded by a layer-specific firing pattern, coincided with fast depolarization, and followed by fast hyperpolarization of these layer 5/6 neurons. Given the known variability of the generators for spike-wave discharge shapes (Slaght et al., 2004), quantifying differences in waveform shape may explain some differences in the type or stage of epilepsy.

Waveform shape differences are also observed within a region. The longer duration of slow oscillation up states in the infragranular layers (below pyramidal cell bodies) compared to supragranular layers (above pyramidal cell bodies) contains information on how the slow oscillation is generated across layers (Fröhlich and McCormick, 2010). By analyzing multielectrode recordings throughout the hippocampus, the hilar region has consistently been observed to have the most sinusoidal oscillations (see ‘hil’ in Fig. 0.2A) (Buzsáki et al., 1986; Konopacki et al., 1988; Montgomery et al., 2009). These results suggest that the electrical properties of these oscillations are nonuniform across the region, even if the whole region contains power at the same frequency.

In addition to differences across cortical layers, waveform shape may also contain information about the neurotransmitters present. Again in the hippocampus, the addition of atropine, which blocks acetylcholine receptors, resulted in more irregular theta oscillations, as characterized by broader distributions in cycle length and trough amplitude (Fig. 0.2B) (Hentschke et al., 2007). In contrast, urethane anesthesia makes the theta oscillation more symmetric . Addition of kainate to hippocampal slices induced gamma oscillations that were more sawtooth-shaped than spontaneously-generated gamma oscillations (Pietersen et al., 2009). The near-instantaneous voltage drop followed by an exponentially decaying voltage rise observed in the kainate-induced gamma oscillations is strikingly similar to the gamma oscillations produced in a previously-mentioned PING model (Mazzoni et al., 2015). In summary, these experiments suggest that the shape of the LFP may index the influence of neurotransmitters on neurophysiology. However, since reports analyzing waveform shape are sparse, it is difficult to generalize these results.

Attempts to explain distinct waveform shapes can inspire models of their physiological generation. A recent study did just this for the transient beta oscillations recorded by MEG in primary somatosensory cortex (S1) and right inferior frontal cortex (IFC) (Fig. 0.2C) (Sherman et al., 2016). The S1 beta waveform is shaped such that the central trough is sharper and more negative than the adjacent troughs, consequently making its flanks relatively steep. It was proposed that the transient oscillations could be generated by nearly synchronous excitatory synaptic burst inputs into the proximal and distal dendrites of pyramidal cells. However, the relative size of the peaks and troughs differed between S1 and IFC; follow up studies incorporating more physiological and architectural features may be able to explain this difference.

For some oscillations, waveform shape may be a surrogate for the population firing rate throughout a period. This relates trivially to slow oscillations in which one extremum is associated with greater local firing whereas the opposite phase is associated with lower firing. Additionally, asymmetric peaks in a slow oscillation period are indicative of strong spiking in that cycle (Lewis et al., 2012), and the sawtooth shape of hippocampal theta oscillations tracks firing rate better than a comparable sinusoid (Fig. 0.2D) (Belluscio et al., 2012). However, the amount of firing rate variance explained by the oscillation waveform in general is unclear, and likely differs by the identity of the oscillator being studied. In a model of cortical gamma oscillations, the population firing rate was a candidate proxy for the biophysically-computed LFP (*R2* > 0.5) (Mazzoni et al., 2015). However, waveform shape may not reflect solely neural processes, as glial membrane potentials are synchronized to slow oscillations and have similar shapes (Amzica and Steriade, 1998, 2000).



**Figure 0.2.** Features of nonsinusoidal waveforms relate to physiology. (a) The shapes of hippocampal theta oscillations change as a function of recording depth. (b) Theta oscillations recorded in mouse hippocampus during exploration without (left) and with (center) addition of atropine. The voltage at each trough is indicated with a dot and the distribution of voltages are represented in histograms (right). Addition of atropine blocks muscarinic acetylcholine receptors and causes the trough voltage to be more variable (broader, black histogram). (c) Transient beta oscillations in human somatosensory cortex recorded by MEG. (top) Examples of raw beta oscillations aligned to the largest trough. (center) The average waveform (shading = standard deviation) has a sharp, steep center transient. (bottom) This waveform shape was reproduced in a model by synchronous excitatory synaptic drive both distal and proximal to the soma. (d) The temporal dynamics of extracellular theta oscillations relate to those of firing rates. The firing histogram color indicates if the spike occurred in the rise of a theta oscillation (red) or the decay (black). The blue line indicates the median voltage of the theta oscillation in each phase bin. The purple line is a sinusoid of comparable frequency. Note that the nonsinusoidal voltage trace is more highly correlated to the population firing rate compared to the sinusoid.

As suggested earlier, the shape of an oscillatory waveform can be analyzed to test whether it is consistent with a proposed model of generation. This has been used, for example, in one modeling study that generated gamma oscillations using two different mechanisms. These two oscillators manifested waveforms that differed in slope ratio (defined above), predicting different waveform shapes (Lee and Jones, 2013). In another example, an oscillation generated by pulsing inhibition has been hypothesized to produce an oscillation with “amplitude asymmetry” (Mazaheri and Jensen, 2010). Amplitude asymmetry occurs when the trough voltage remains constant while the peak voltage fluctuates (or vice versa). Thus it has been proposed that pulsing inhibition is the underlying mechanism of some MEG oscillations projected to occipital, central, and parietal areas that have this property (Nikulin et al., 2007; Mazaheri and Jensen, 2008, 2010; van Dijk et al., 2010). This model is consistent with known inhibitory feedback from the neocortex and thalamus (Mazaheri and Jensen, 2010), but direct empirical evidence is needed to confirm this model.

Causal evidence of the computational importance of oscillatory waveform shape comes from studies applying oscillatory neurostimulation. Modifying the shape of the stimulating waveform, while preserving amplitude and frequency, resulted in changes in the efficiency of entraining local population spiking in slices (Fröhlich and McCormick, 2010) and alpha oscillations in human EEG (Dowsett and Herrmann, 2016). In both cases, it was concluded that the steep slopes of the nonsinusoidal stimulation are key in entraining the network, reminiscent of a previous modeling result showing that nonsinusoidal oscillators synchronize faster to one another compared to more sinusoidal oscillators (Somers and Kopell, 1993). Relatedly, rectangular waves induce seizures more reliably than sine waves for electroconvulsive therapy (Merritt, 1938; Abrams, 2002), and sine wave stimulation is associated with greater memory loss and more intense seizures (Weiner et al., 1986a, 1986b). In summary, the effects of neurostimulation vary greatly with the stimulating waveform, suggesting that electrical waveforms generated by the brain may also impact neural computation in different ways.

**Oscillatory waveform shape relates to disease and behavior states**

Two recent studies have compared the shape of neural oscillations between disease states. In anesthetized rats, the relative duration of up and down states were measured in parietal cortical slow oscillations (Ouedraogo et al., 2016). There was no difference in slow oscillation frequency between rats developing epilepsy compared to control animals. However, the rats developing epilepsy had relatively longer up states. Recently we analyzed primary motor cortical ECoG from patients with Parkinson’s disease who had undergone implantation of a permanent deep brain stimulator (DBS), as explained in detail in Chapter 1. Oscillations were most asymmetric in regards to peak and trough sharpness in recordings from untreated Parkinsonian patients compared to those same patients when their DBS was turned on (Fig. 0.3A). Sharpening of oscillatory beta extrema may reflect an increase in synchrony of synaptic bursts (Sherman et al., 2016) thought to be pathological in Parkinson’s disease.

There is mounting evidence that the prominent hippocampal theta oscillation shape is altered with behavior. In particular the aforementioned sawtooth shape of hippocampal theta has been reported to become more asymmetric (i.e., approaching the instantaneous voltage change that characterizes a pure sawtooth) when a rat is running, compared to during immobility (Hentschke et al., 2007), lever pressing (Buzsáki et al., 1985), or REM sleep (Belluscio et al., 2012) (Fig. 0.3B). This change in the asymmetry of hippocampal theta oscillations during running must reflect a change in the rhythmic neural computation. Future studies could identify the mechanisms associated with changes in theta asymmetry and what significance this has for running behavior. A similar analysis on theta oscillations was performed during memory encoding periods (Trimper et al., 2014). During encoding of objects that were subsequently remembered (compared to subsequently forgotten), the rat’s hippocampal theta oscillation was more asymmetric (Fig. 0.3C). There was no accompanying change in theta frequency or amplitude. The authors theorized that this elongation of the theta oscillation’s falling slope improved memory by enhancing CA3-CA1 gamma coherence. Future studies can test this hypothesis by using electrical or optogenetic stimulation to manipulate the shape of the theta waveform in CA1.

**Concluding remarks**

Here I reviewed a broad literature showing that oscillations have diverse waveform shapes. These nonsinusoidal features likely relate to physiology, making it theoretically possible to infer physiology from waveform shape. This idea has been hinted at or directly mentioned in several past reports, however, such reports of waveform shape have been brief and sparse in the literature of neural oscillations. While relatively novel in neuroscience, nonsinusoidal oscillations emerge in other physical phenomena with associated methods for addressing these features. For example, the chemical processing industry applies curve-fitting algorithms to identify nonsinusoidal waveforms in control loops.

Future efforts in experimental design, analytical methods development, and computational modeling should explicitly probe how differences in waveform shape relate to differences in physiology. For example, rhythmic stimulation experiments (electric, magnetic, optogenetic, etc.) can vary the stimulating waveform and assess behavioral or physiological differences. Additionally, simultaneous recordings of field potentials and neuronal spiking will help us quantify relationships between waveform shape, synchrony, and other spiking features (see Chapter 3). It may even be possible to move past the sinusoidal assumptions of the Fourier transform and toward more biologically-informed decomposition methods, perhaps consisting of a “dictionary” of neurophysiological basis functions.

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**Figure 0.3.** Features of oscillatory waveforms relate to behavior and disease. (a) The sharpness of the peaks and troughs of motor cortical beta oscillations were measured in Parkinson’s disease (PD) patients. The overlap in peak and trough sharpness distributions is lower in PD patients with an implanted DBS turned off (left) compared to when it is turned on (right). In other words, the sharpness ratio between the peaks and troughs is greater in untreated PD patients, as visualized by a separation in the distributions of peak and trough sharpness. (b) Hippocampal theta oscillations in rats are more asymmetric while the rats are running (top) compared to when the rat is sleeping (bottom). During running, theta oscillations generally have a steeper rise to the peak and a more gradual decay to the trough. (c) Hippocampal theta oscillation symmetry also differed in rats based on memory performance. During a successful encoding period of an object, the theta oscillation was more asymmetric in that its falling phase was extended and its rising phase was shortened.

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