Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Are Beta Phase-Coupled High-Frequency Oscillations and Beta Phase-Locked Spiking Two Sides of the Same Coin?

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Review of Yang et al.

Changes of oscillatory patterns in the basal ganglia and in subcortico-cortical motor loops are a hallmark of Parkinson's disease (PD; Hammond et al., 2007). However, the neuronal mechanisms underlying these spectral dynamics and how they contribute to motor symptoms remain to be clarified. A popular hypothesis is that beta oscillations (13–30 Hz) in the subthalamic nucleus (STN) are associated with impaired motor performance, whereas gamma (60–90 Hz) and high-frequency oscillations (HFOs; 200–500 Hz) are associated with normal movement (Oswal et al., 2013). Notably, there are cross-frequency interactions in the parkinsonian STN. The amplitude of HFOs is modulated by the phase of beta oscillations, and this phase–amplitude coupling is increased when patients are in an unmedicated (OFF) state (Lopéz-Azcárate et al., 2010; Özkurt et al., 2011). Furthermore, it was observed that beta–HFO phase–amplitude coupling correlates positively with motor symptom severity, whereas baseline HFO power and modulation of HFO power during movement are strongest in patients with relatively good motor performance (Lopéz-Azcárate et al., 2010; Wang et al., 2014). Thus, it seems plausible that beta oscillations exert an adverse effect on HFOs, which would otherwise facilitate movement.

Despite its potential importance for motor control, the mechanisms generating beta–HFO phase–amplitude coupling remain elusive. A recent study by Yang et al. (2014) in *The Journal of Neuroscience* is an important first step toward understanding phase–amplitude coupling in PD. The authors investigated whether beta–HFO phase–amplitude coupling might emerge as a consequence of beta spike-phase locking, i.e., a tendency for spikes to occur at a specific phase within the beta cycle. Thus, this interesting paper links neuronal oscillations to spiking in the STN, which has been shown to encode diverse aspects of motor state, such as the type of movement (active or passive) or the muscles involved (extensor or flexor; Magariños-Ascone et al., 2000).

The data were recorded in PD patients undergoing surgery for deep brain stimulation (DBS). A combination of micro- and macro-electrodes was gradually inserted along the trajectory of the DBS electrode so that recordings of both local field potentials and spiking activity in and around the STN could be obtained. The authors then analyzed the spectral and spatiotemporal characteristics of phase–amplitude coupling and spike-phase locking.

Yang and colleagues (2014) found both the amplitude of HFOs and spiking to be significantly coupled to the phase of beta oscillations, and both couplings showed a similar spatial distribution. Phase–amplitude coupling and spike-phase locking were most pronounced near the dorsal border of the STN. This was also the site most frequently selected for DBS based on the therapeutic window, i.e., the span between the minimum voltage producing clinical improvement (window entry voltage) and the minimum voltage producing side effects. In addition, the authors found a negative correlation between phase–amplitude coupling strength for each electrode contact and its therapeutic window entry voltage. This finding suggests that phase–amplitude coupling is strongest at the most efficient stimulation targets. These findings are remarkable because they point to beta–HFO phase–amplitude coupling as a spatial biomarker in DBS target localization, emphasizing its clinical relevance. Unfortunately, the direct importance of beta–HFO phase–amplitude coupling for PD symptoms remains unclear, because the authors did not assess correlations between phase–amplitude coupling and clinical ratings of symptom severity.

Intriguingly, the authors could not find any spatiotemporal association between phase–amplitude coupling and spike-phase locking, even though both spikes and HFOs were locked to beta band oscillations and had a similar topography. Phase–amplitude coupling and spike-phase locking were uncorrelated across recording sites with respect to the percentage of occurrence and coupling strength. Moreover, HFOs and spikes significantly differed in their preferred beta phase. HFOs tended to occur near beta peaks, whereas spikes were more frequent

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near the troughs. Importantly, Yang and colleagues (2014) further tested for a temporal relationship between phase–amplitude coupling and spike-phase locking. HFO power did not increase around spike times, and HFO activity did not systematically precede or follow spikes. Of course, one has to keep in mind that absence of proof is not proof of absence. Nevertheless, the experimental design and the sound data analysis are compelling and indicate that spike-phase locking and phase–amplitude coupling might be unrelated phenomena in the parkinsonian STN.

The finding that spike-phase locking and beta–HFO phase–amplitude coupling are uncorrelated is particularly interesting with regard to the unknown origins of HFOs. In fact, most researchers intuitively suspect hypersynchronized spiking to be the cause of HFOs. What other process is both fast and strong enough to produce a high-frequency, extracellular potential that can be detected by the comparably large contacts of a DBS electrode? Theoretically, hypersynchronized spiking could be locked to a specific phase within the beta cycle and thereby produce beta–HFO phase–amplitude coupling. The results by Yang and colleagues (2014), however, suggest that phase–amplitude coupling and spiking may not be two sides of the same coin. Notably, this idea is supported by recent data from other labs. Wang et al. (2014) investigated subthalamic HFOs recorded during DBS surgery and found no qualitative change in HFO characteristics after removing spikes from the raw data traces. Thus, local spiking does not seem to contribute significantly to HFOs and their coupling to beta oscillations.

Importantly, these observations do not exclude the possibility that spiking is important for HFO generation on a larger spatial scale. Because microelectrodes sample only a limited anatomical area, it is conceivable that they miss multiunit activity related to HFOs and beta–HFO phase–amplitude coupling. Ultimately, this issue can only be resolved by recording more cells, which is currently not feasible in DBS surgery. High-density probes used in animal recordings might be able to provide an answer (Nicolelis et al., 2003), but currently it is not even known whether subthalamic HFOs and beta–HFO phase–amplitude coupling exist in either rodent or primate models of PD.

Despite these limitations, the lack of association between spikes and subthalamic HFOs remains striking, particularly given recent literature on HFOs in epilepsy. In the dentate gyrus of epileptic mice, there seems to be a strong relationship between synchronized discharge of principal cells and pathological fast ripples (Bragin et al., 2002). It is important to note, however, that hippocampal fast ripples hardly resemble subthalamic HFOs in terms of stability, frequency content, or coupling to slower oscillations. Hence, it seems reasonable to assume that subthalamic and epilepsy-related HFOs reflect different neuronal processes.

Another important issue related to the origins of HFOs is the distribution of HFO peak frequencies. Given the results of previous studies, this distribution might be bimodal. Two recent studies demonstrated the existence of two distinct high-frequency rhythms: a slow rhythm of ~260 Hz and a fast rhythm of ~340 Hz (López-Azcárate et al., 2010; Özkurt et al., 2011). A similar distinction has been suggested for the beta band (Priori et al., 2004). The slow HFO rhythm dominates under dopamine depletion while the fast rhythm is enhanced under medication. Since the relative strengths of these two rhythms reflect the medication state very reliably, they could turn out to be powerful biomarkers (Özkurt et al., 2011). Currently, it remains unclear whether slow and fast HFOs are produced by different neuronal populations or by two different processes co-occurring within the same population of neurons.

In conclusion, the study by Yang et al. (2014) provides valuable new information for comprehending the complex dynamics of oscillatory activity in the parkinsonian STN. To date, research concerning the pathophysiology of PD has concentrated on beta and gamma oscillations, whereas the role of HFOs has only recently been put into focus. The findings of Yang and colleagues (2014) give further support to the importance of HFOs and provide a starting point for further investigation of their origin and functional relevance.

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