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High-frequency oscillations – Where we are and where we need to go

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ABSTRACT

High-frequency oscillations (HFOs) are EEG field potentials with frequencies higher than 30 Hz; commonly the frequency band between 30 and 70 Hz is denominated the gamma band, but with the discovery of activities at frequencies higher than 70 Hz a variety of terms have been proposed to describe the latter (Gotman and Crone, 2011). In general we may consider that the term HFO encompasses activities from 30 to 600 Hz. The best practice is to indicate always explicitly the frequency range of the HFOs in any specific study. There are numerous types of HFOs: those in normal brain appear to facilitate synchronization and information transfer necessary for cognitive processes and memory, while a particular class of HFOs in the brain of animals and people with epilepsy appears to reflect fundamental mechanisms of epileptic phenomena and could serve as biomarkers of epileptogenesis and epileptogenicity in abnormal conditions such as epilepsy. A better understanding of the significance of HFOs depends on a deeper analysis of the mechanisms of generation of different kinds of HFOs, that typically are at the crossroads between intrinsic membrane properties and neuronal interactions, both chemical and electrical. There is still a lack of understanding of how specific information is carried by HFOs and can be operational in normal cognitive processes such as in working and long-term memory and abnormal conditions such as epilepsy. The complexity of these processes makes the development of relevant computational models of dynamical neuronal networks most compelling.

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Rhythms are a basic feature of all life (Buzsáki, 2006). Electrical biorhythms of the brain have been used to study basic mechanisms of normal and abnormal human behavior since the advent of the EEG three-quarters of a century ago (Berger, 1929). Recent interest has focused on wide-band EEG recordings to measure high-frequency oscillations (HFOs) in the range of 80–600 Hz (Worrell and Gotman, 2011; Staba and Bragin, 2011). There are undoubtedly many physiological and pathological manifestations of HFOs that correspond to different types of neuronal generators. Among the former are ripples (80–200 Hz) recorded from normal hippocampus and other parahippocampal structures, and faster neocortical oscillations (>250 Hz), such as those recorded from barrel cortex of the rat. Considerable recent interest has focused on fast ripples (250–600 Hz) which appear to reflect pathological processes related to epileptogenicity (Bragin et al., 1999; Staba and Bragin, 2011; Worrell and Gotman, 2011). Because ripple frequency HFOs are generated in epileptic dentate gyrus, where in normal animals ripples do not occur, it is clear that pathological HFOs (pHFOs) are not limited to the fast ripple frequency band (Engel et al., 2009). Identifying and characterizing these different types of HFOs is of paramount importance in using them to understand fundamental mechanisms of normal cognitive function, and pathological processes such as epileptogenesis and epileptogenicity. Distinguishing normal oscillations from pHFOs is also important in efforts to use the latter as biomarkers for epilepsy, particularly to

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localize and determine the boundaries of the epileptogenic region for surgical treatment. This workshop has focused on HFOs as both normal and pathological processes.

Possible approaches to distinguishing normal from pathological HFOs could include their relationship to interictal EEG spikes; responses to perturbation of the system such as sleep–wake cycle, stimulation, and drugs; metabolic differences that might be measured by functional magnetic resonance imaging (fMRI) or optical imaging, and their association with areas of atrophy or lesion on MRI. As indicated in the paper by Jacobs et al., in this volume, ripple frequency HFOs appear more likely to identify the epileptogenic region than might be expected from microelectrode studies in animals. Perhaps, due to dipole relationships or other features, the normal HFOs are more likely to be filtered out by macroelectrodes used in clinical studies.

1. Normal HFOs and cognitive function

The role that HFOs may play in neurocognitive processes has attracted particular attention: oscillations around 40 Hz in the visual cortex associated with visual perception (reviewed in Slinger and Gray (1995)), and in the sensorimotor cortex related to motor activity (Murthy and Fetz, 1996) were put in evidence. The former were proposed to form the mechanism by which various features of a visual scene may be bound together into a percept (“binding hypothesis”). It was also shown that HFOs may operate as a general mechanism that is capable of binding together, by a process of phase synchronization, not only the firing of neurons at the local level, but also neural activities of spatially separate cortical areas (Roelfsema et al., 1997). Several studies support the hypothesis that HFOs may play a role in encoding information, as the study of Tallon-Baudry et al. (1998) who found an increase of gamma power (20–80 Hz), in subjects performing a visual delayed-matching-to-sample task during the period where the subjects memorized information, particularly in occipitotemporal and frontal sites. Similarly Sederberg et al. (2007) recorded intracranial EEG while subjects encoded verbal memories for nouns, and found that gamma oscillations (44–64 Hz), in the hippocampus and the left temporal and frontal cortices, predict successful encoding of new verbal memories for nouns. In the same context Fell et al. (2006) showed that successful memory formation for words is accompanied within 1 s by a transient enhancement of phase synchronization in the gamma frequency range (32–48 Hz) between rhinal cortex and hippocampus, as well as enhanced coupling in the sub-gamma range. Such studies demonstrate that HFOs (30–120 Hz) are not only relevant to binding of visual perceptions but have a broader connotation and appear to underlie several features of information processing and both working and long-term memory (Jensen et al., 2007). As discussed also by Fries (2009) gamma-band synchronization should be considered a general operational mode of cortical processing of information working through a mechanism of entrainment of neuronal networks that can promote the transfer of relevant information between different neuronal networks. Evidence for this feature of HFOs was presented at the workshop by Born (Diekelmann and Born, 2010) showing that spindle activity and HFOs (ripples) increase during the “up-state” of the slow oscillation, characteristic of sleep, and become suppressed during the “down-state” of the slow oscillation. Studies in man using large-scale microelectrode recordings showed low (40–80 Hz) and high (80–120 Hz) oscillations during slow-wave sleep associated with cortical “up-states” often within 100 ms after hippocampal ripple/sharp wave complexes (Le Van Quyen et al., 2010). The hypothesis is that during the “up-state” the ripples and spindles would provide a mechanism by which information would be transferred from the hippocampal formation to the neocortex. The importance of ripples in this process is supported by the findings of Ego-Stengel and Wilson (2010) who showed that disrupting selectively neuronal activity during ripple events, by stimulating hippocampal afferents in the rat, impairs spatial learning.

Another line of experimental evidence linking HFOs (ripples) and memory processes is the finding in rodents that during sleep there is a *re-activation*, *or replay*, of patterns of activity of assemblies of neurons that were previously active during memory acquisition in the awake state (Wilson and McNaughton, 1994). This replay appears preferentially during hippocampal “sharp wave-ripple complexes” (Lee and Wilson, 2002), as these sharp waves are associated with HFO ripples (200 Hz) and may be temporally correlated with slow wave sleep cortical spindles (for a detailed discussion see Buzsáki, 2006, pp. 342–355). It appears that slow oscillations drive the ripples that are associated with hippocampal re-activation; thus it has been hypothesized that spindle–ripple complexes would lead to plastic synaptic changes of long duration and to the storage of information in the neocortex. This would form the main mechanism for the transfer of memory traces from the hippocampus to the neocortex (Molle and Born, 2009; Marshall and Born, 2007). The main challenge is to understand how specific information is carried by spindle–ripple complexes.

2. pHFOs and epilepsy

A characteristic of most non-genetic (idiopathic) epileptic brain tissue is the presence of synchronously bursting neurons. Whereas up to 90% of neurons may participate in these synchronous events in certain acute experimental conditions such as the penicillin cortical focus (Matsumoto and Ajmone-Marsan, 1964), less than 10% of neurons burst synchronously in chronic animal models and humans with epilepsy and have been difficult to record (Babb and Crandall, 1976). pHFOs appear to be field potentials of these unique epileptic neuronal events and, therefore, provide a much more robust means to identify epileptogenic tissue (Bragin et al., 2011). As such, they not only offer a powerful approach to understanding fundamental neuronal mechanisms underlying epileptogenesis and ictogenesis (seizure generation), but may also serve as biomarkers of epileptogenesis, the development and progression of brain tissue capable of generating spontaneous seizures, and of epileptogenicity, the presence and severity of an epileptic condition, for clinical purposes (Engel, 2011). Biomarkers of epileptogenicity identify the presence and severity of an epilepsy condition, and not only would help identify epileptogenic tissue for surgery, but if noninvasive measures were possible, they would permit definitive differential diagnosis of epilepsy from acute symptomatic seizures so treatment can begin immediately, and from non-epileptic seizures, sparing the need for long-term monitoring in some patients. Biomarkers of epileptogenicity might also make it possible to assess the efficacy of therapeutic interventions without waiting for another seizure to occur, which could be associated with significant morbidity or mortality. Biomarkers of epileptogenesis would make it possible to identify patients at risk of epilepsy following a potential epileptogenic insult for validating potential antiepileptogenic interventions, and diagnosing progressive and possibly pharmacoresistant epilepsy disorders to facilitate early surgical referral. In addition, pHFO biomarkers could be used to design cost-effective rapid-throughput screening measures for new antiepileptic and antiepileptogenic compounds, and noninvasive identification of pHFO biomarkers would reduce the cost of clinical trials. Potential noninvasive approaches to measuring pHFOs include scalp EEG recording, magnetoencephalography (MEG), and simultaneous EEG-fMRI. It should be noted that recording HFOs in EEG recordings at the human scalp presents considerable difficulties

due to the possible contamination with EMG. Nonetheless gamma oscillations (40–80 Hz) and faster ripples (>80 Hz) were recorded in scalp EEG of epileptic patients, and might be inter-ictal markers for the seizure-onset-zone (Andrade-Valença et al., 2011). The use of MEG may present advantages in this respect. In studies at the level of the human scalp it is necessary to carefully control the electrode montage, and to consider Laplacian derivations and appropriate signal analysis, such as Independent Component Analysis (ICA).

In summary in the Workshop it was emphasized that it is useful to take into consideration the following items in characterizing HFOs in practice:

(i) To name the frequency range of the HFO by always indicating the latter in parentheses, as for example: HFO (80–150 Hz) in order to avoid misinterpretations.
(ii) To indicate whether the HFO in a particular case is a transient (burst-like) or continuous (steady-state) phenomenon, and whether it is phase-locked to a stimulus or event-related but not phase-locked;

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